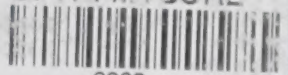




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Alkaloids: Chemi..

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THE ALKALOIDS

Chemistry and Physiology

VOLUME III

THE ALKALOIDS

Chemistry and Physiology

Edited by

R. H. F. MANSKE

*Dominion Rubber Research Laboratory
Guelph, Ontario*

H. L. HOLMES

*The Carwin Company
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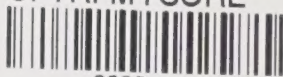
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PREFACE

Again we take this opportunity to express our thanks for the reception which chemists have accorded our efforts to review for them the chemistry of the alkaloids. We are acutely conscious of the almost unprecedented activity in this field and aware that the volumes as published often and inevitably cannot include the most recent material. We hope to publish a supplement which will take care of such matters, and we invite authors of papers on alkaloids to send us reprints of all material which has not been included in the printed volumes.

The continued efforts and cooperation of the contributors to this series are gratefully acknowledged.

R. H. F. M.

H. L. H.

June, 1953

CONTENTS

PREFACE	v
-------------------	---

The Chemistry of the Cinchona Alkaloids

BY RICHARD B. TURNER AND R. B. WOODWARD, *Harvard University,
Cambridge, Massachusetts*

I. Determination of Structure	2
II. Reactions of the Alkaloids	8
III. Stereochemistry	24
IV. Synthesis	35
V. Minor Alkaloids	50
VI. Biogenetic Relationships	54
VII. References	58

Quinoline Alkaloids, other than those of Cinchona

BY H. T. OPENSHAW, *University of St. Andrews, St. Andrews, Scotland*

I. Introduction	66
II. Echinopsine	66
III. The Furoquinoline Group	69
IV. Alkaloids of Angostura Bark	80
V. References	98

The Quinazoline Alkaloids

BY H. T. OPENSHAW, *University of St. Andrews, St. Andrews, Scotland*

I. Introduction	101
II. Vasicine (Peganine)	102
III. Alkaloids of <i>Dichroa febrifuga</i> , Lour	112
IV. References	117

Lupin Alkaloids

BY NELSON J. LEONARD, *University of Illinois, Urbana, Illinois*

I. Occurrence and Constitution	120
II. Extraction Procedure	128
III. Structure of the Alkaloids	130
IV. Stereochemistry of the C ₁₅ -Lupin Alkaloids	191
V. References	192

The Imidazole Alkaloids

BY A. R. BATTERSBY AND H. T. OPENSHAW, *University of St. Andrews,
St. Andrews, Scotland*

I. Bases Related to Histidine	202
II. The Jaborandi Alkaloids	206
III. Pilocarpine and Isopilocarpine	207
IV. Pilocarpidine	228

V. Pilosine	230
VI. Tables of Physical Constants of the Jaborandi Alkaloids, Their Derivatives and Degradation Products	233
VII. References	242

The Chemistry of Solanum and Veratrum Alkaloids

By V. PRELOG AND O. JEGER, *Laboratory of Organic Chemistry,
Eidgen. Technische Hochschule, Zurich, Switzerland*

I. Introduction	248
II. Solanum Alkaloids	249
III. Veratrum Alkaloids	270
IV. References	309

β -Phenethylamines

By L. RETI, *ATANOR Compañía Nacional para la Industria Química,
Sociedad Anónima Mixta, Buenos Aires, Argentina*

I. Introduction	313
II. Biosynthesis	315
III. Chemistry of the β -Phenethylamines Found in Plants	316
IV. Pharmacology of the β -Phenethylamines	329
V. References	334

Ephedra Bases

By L. RETI, *ATANOR Compañía Nacional para la Industria Química,
Sociedad Anónima Mixta, Buenos Aires, Argentina*

I. Introduction	339
II. Occurrence	340
III. Extraction and Separation	343
IV. Detection and Determination	344
V. Physical and Chemical Properties	344
VI. Constitutional and Spatial Configuration	349
VII. Synthesis of the Ephedra Bases	351
VIII. Pharmacology	353
IX. References	355

The Ipecac Alkaloids

By MAURICE-MARIE JANOT, *Faculty of Pharmacy, University of Paris, France*

I. Introduction	363
II. Interrelation of the Alkaloids	364
III. Structure of the Alkaloids	366
IV. Extraction and Industrial Preparation of the Alkaloids	382
V. Color Reactions	384
VI. Table of Physical Constants	384
VII. Physiological and Therapeutical Properties	390
VIII. References	391

Author Index	395
------------------------	-----

Subject Index	416
-------------------------	-----

CHAPTER 16

The Chemistry of the Cinchona Alkaloids

RICHARD B. TURNER AND R. B. WOODWARD

Harvard University, Cambridge, Massachusetts

	<i>Page</i>
I. Determination of Structure	2
II. Reactions of the Alkaloids.	8
1. The C.8-C.9 System	8
a. The Cinchona Toxines.	13
b. The Anhydro Bases	13
c. The Cinchona Ketones.	15
d. The <i>Hetero</i> Bases	17
2. Reactions Primarily Involving the Vinyl Group	19
a. Simple Addition and Cleavage Reactions.	19
b. Migration of the Double Bond	20
c. Formation of the Niquine Bases.	21
3. Miscellaneous Transformations	22
a. Demethylation	22
b. Reactions of the <u>Pyridine</u> and <u>Quinoline</u> Rings	22
c. Formation and Reactions of the <u>Desoxy</u> Bases	23
d. Removal of the Oxygen Atom at C.6'	24
e. Reactions at N.1	24
f. Metabolic Reactions.	24
III. Stereochemistry	24
1. C.3 and C.4.	25
2. C.8	28
3. C.9	30
4. Direct Interconversions.	34
IV. Synthesis	35
1. The Quinoline Portion	37
2. The Quinuclidine Portion.	38
3. 4-Quinolylketones and the Toxines.	42
4. Conversion of the Toxines to the Alkaloids	45
5. Total Synthesis of Dihydroquinine.	47
6. Total Synthesis of Quinine	48
V. Minor Alkaloids	50
1. Cinchonamine.	50
2. Quinamine and Conquinamine.	51
VI. Biogenetic Relationships	54
VII. References.	58

The cinchona alkaloids are found in the bark of *Cinchona* and *Remijia* species, which are indigenous to the high (5000-8000 feet) eastern slopes of the Andes from 10° N to 20° S latitude (1). The great demand

for the alkaloids in medicine has led to extensive and successful cultivation and breeding in India, Ceylon, and the Dutch East Indies (2).

Cinchona preparations were introduced into medical use in Europe in the early seventeenth century, and were popularized through the efforts of the wife of the then Spanish Viceroy of Peru, the Countess of Chinchon, who in 1638 was successfully treated for malaria through administration of the hitherto little known remedy. Almost two hundred years later, one of the most intensive chemical investigations of the nineteenth century began, with the isolation of a crude mixture of crystalline alkaloids from the bark by Gomes in Portugal in 1810, and of pure quinine and cinchonine by Pelletier and Caventou in 1820 (3). Subsequently, upwards of two dozen further bases have been isolated from *Cinchona* and *Remijia* species; of these only quinidine (van Heijningen, 4) and cinchonidine (Winckler, 5) need be mentioned here.

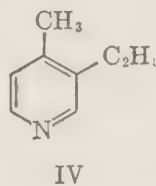
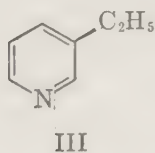
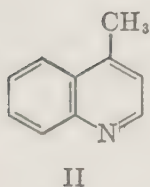
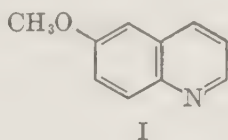
I. Determination of Structure

The investigations which culminated in the determination of the structures of the cinchona alkaloids have long been established as a classic of organic chemistry. It is worthy of note that much of our knowledge of the chemistry of quinoline and pyridine derivatives, and thence, of heterocyclic compounds in general, had its inception in the results of degradative studies on quinine and its congeners. Then, as now, the study of natural products enriched the body of general knowledge in the science, and pointed the way to new departures in the theory and practice of organic chemistry.

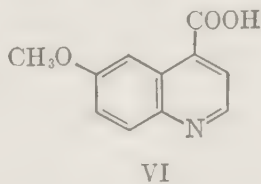
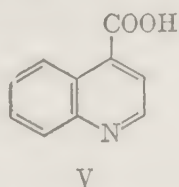
Strecker is credited with having first established the empirical formula $C_{20}H_{24}N_2O_2$ for quinine (6). Later, Skraup showed that cinchonine possesses the formula $C_{19}H_{22}N_2O$ (7). Both alkaloids were shown to be diacidic through analyses of salts. The nitrogen atoms were shown to be tertiary by the preparation of isomeric tertiary ethiodides (6, 8, 9). Hesse showed that quinine and cinchonine, as well as quinidine and cinchonidine, are converted by warm acetic anhydride into monoacetyl derivatives which are hydrolyzed by alcoholic potash to the original bases (10). When it became clear that both nitrogen atoms were tertiary these experiments demonstrated the presence of an hydroxyl group in the alkaloids. This conclusion was confirmed by the transformation of the alkaloids into chlorides ($OH \rightarrow Cl$) through the action of phosphorus pentachloride in chloroform (11-14). The cinchona bases were shown to be rapidly attacked by permanganate, and to form addition products with halogen acids (14-21) and bromine (12, 14, 22, 23). These indications of the presence of a double bond were confirmed, and the function was shown to be incorporated as a vinyl group, through oxidation of the

alkaloids to carboxylic acids ($-\text{CH}=\text{CH}_2 \rightarrow -\text{COOH}$) and formic acid (24–31).

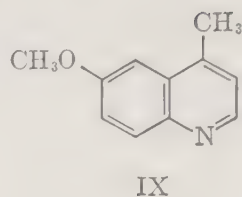
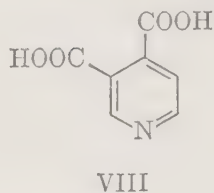
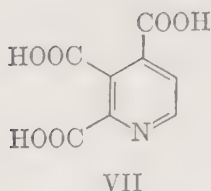
The first insight into the nature of the main framework of the alkaloidal structures was obtained through the study of the products resulting when the bases were subjected to destructive fusion with caustic potash. Quinoline was obtained for the first time when cinchonine was so treated (32, 33). The correct structure for the key degradation product was suggested by Körner (34), and established through syntheses of the base by Koenigs (35), by Baeyer (36, 37), and by Friedländer (38). From quinine, by similar methods, an oxygenated base was obtained (39), which was shown to be 6-methoxyquinoline (I) (40). The attachment of a substituent in the γ -position of the quinoline nucleus in these alkaloids was indicated by the isolation (33) and proof of structure (41–45) of lepidine (II). The formation of β -ethylpyridine (39, 46) (III) and β -collidine (47, 48) (IV) in the alkali degradations stimulated work on the chemistry of pyridine bases.



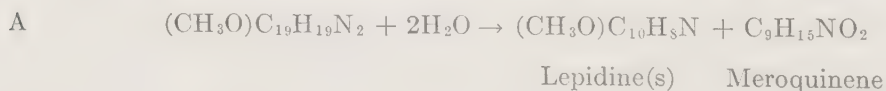
The oxidation of the cinchona alkaloids also led to quinoline and pyridine derivatives. From cinchonine, and cinchonidine, by oxidation with nitric, or chromic acid, cinchoninic acid (V) was obtained (16, 49–51) and related to lepidine (41, 42). Similarly, quinine and quinidine were converted to quininic acid (52, 53), which was shown to have the structure (VI). Further oxidation of the quinoline acids was shown to lead



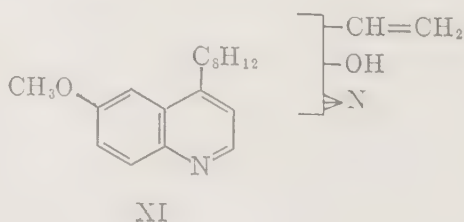
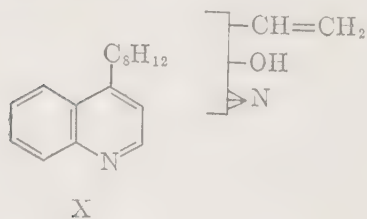
to pyridine-2,3,4-tricarboxylic acid (VII) (16, 51, 52, 53) and cinchome-ronic acid (VIII), which were also obtained directly from the alkaloids under drastic oxidative conditions (54, 55).



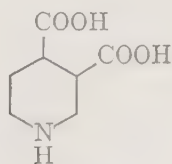
The isolation of quinoline and its congeners from oxidation and drastic alkali degradations suggested the presence in the alkaloids of an intact quinoline nucleus, but other evidence was needed to exclude the possibility that the fully aromatic nuclei arose from hydroaromatic precursors by oxidative or dehydrogenative processes. When the chlorides derived from cinchonine and cinchonidine were dehydrohalogenated by alcoholic potash, a new base, cinchene, $C_{19}H_{20}N_2$, was formed (12, 56); in a similar manner, the base quinene, $C_{20}H_{22}N_2O$, was formed from quinine and quinidine. When quinene and cinchene, or their salts, were heated with water or acids under carefully controlled conditions, 6-methoxy-lepidine (IX) and lepidine (II), respectively, were obtained (57). Later, it was found that the cleavage proceeded sufficiently smoothly when the anhydro bases were heated with 20% aqueous phosphoric acid at 170–180° to permit isolation of a fragment which contained all of the atoms of the original alkaloids in excess of those which appeared as quinoline derivatives (58). The same substance, $C_9H_{15}NO_2$, was obtained from quinine and from cinchonine; it was named meroquinene (Gr. *μερος*, a part), and became a key substance in the elucidation of the constitution of the non-aromatic “second half” of the cinchona bases. It was clear that the cleavage of quinene and cinchene had followed the course A,[†]



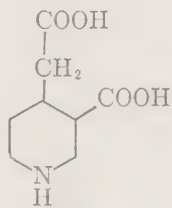
and that for the first time, strong positive evidence was available for the presence of an intact quinoline ring in the alkaloids themselves. Confirmation of this view was soon obtained when the hydrogen-rich meroquinene was found among the products of the direct oxidation of cinchonine (59). It was now possible to ascribe to cinchonine and quinine the structures (X) and (XI) with confidence.



The arrangement of atoms in the non-aromatic portion of the molecules was deduced from the study of meroquinene, and three other products which had previously been isolated from the complex mixtures obtained by oxidation of the alkaloids. The first of these was cincholoipon, $C_9H_{17}O_2N$, obtained by oxidation of cinchonine (60); it was not realized until later that the degradation product was in fact derived from dihydrocinchonine present in the natural base (61, 62). The second was cincholoiponic acid, $C_8H_{13}NO_4$ (60, 63), and the third, loiponic acid, $C_7H_{11}NO_4$ (62). Cincholoipon was found to contain an imino and a carboxyl group, and was transformed on distillation with zinc dust to β -ethyl pyridine (III). Cincholoiponic acid and loiponic acid were iminodicarboxylic acids. Meroquinene resembled cincholoipon in containing an imino and a carboxyl group (58). It was transformed smoothly into β -collidine (IV) when it was treated with dilute hydrochloric acid at 240° , and was oxidized by cold dilute acidic permanganate to cincholoiponic acid. By reduction with zinc and fuming hydriodic acid, it was converted into cincholoipon. Finally, cincholoiponic acid was converted directly by oxidation with permanganate to loiponic acid (62). Thus, all of these degradation products were interrelated, and shown to be 3,4-disubstituted piperidine derivatives, a view which was confirmed when loiponic acid, the simplest of them, was shown to be epimerized by potash at 200° to a hexahydrocinchomeronic acid (XII) available by synthesis (65). The most direct deduction from these facts was that

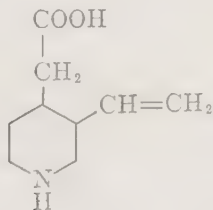


XII

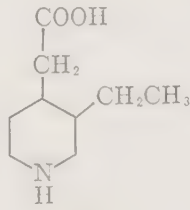


XIII

cincholoiponic acid, meroquinene, and cincholoipon could be formulated as (XIII), (XIV) and (XV), respectively. Unfortunately, the conver-

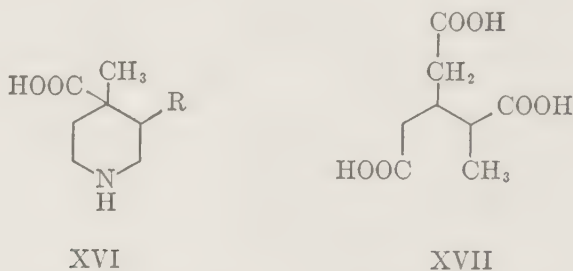


XIV



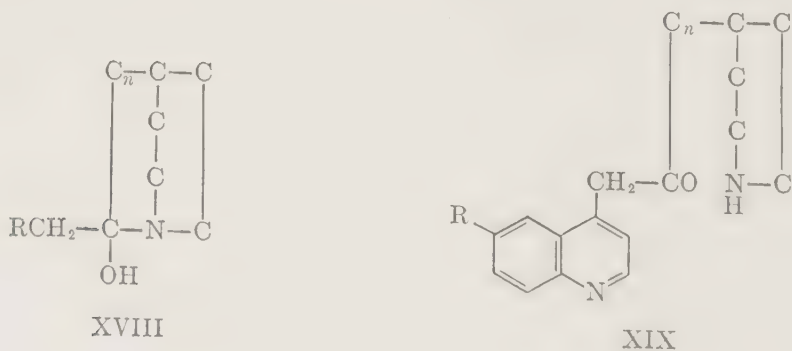
XV

sion of cincholoiponic acid to loiponic acid had proceeded in so low a yield that the possibility could not be excluded that the simpler acid had been derived from an impurity in the cincholoiponic acid, or by unusual processes. Consequently, it was not possible to dismiss rigorously structures such as (XVI, $R = C_2H_5$, C_2H_3 or $COOH$) for the degradation products (66). The degradation of cincholoiponic acid by exhaustive methylation and potash fusion to the acid (XVII), whose structure was proven by synthesis, afforded further support for the structure (XIII) (67), although the reaction sequence was sufficiently unusual to warrant some skepticism about the value of the evidence in structural arguments.

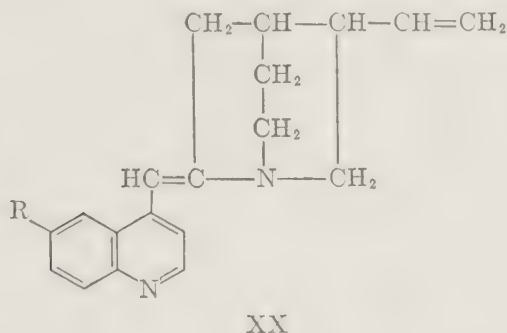


None the less the expressions (XIII), (XIV) and (XV) had gained general acceptance shortly after the turn of the century, and were finally shown conclusively to be correct through the synthesis of cincholoiponic acid by an unambiguous route (68, 69).

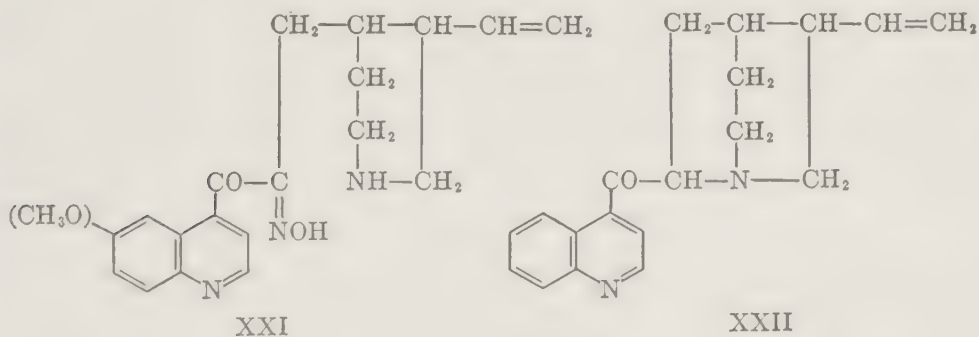
It remained to establish the manner of linkage of the two portions of the molecule represented by the known cleavage products. von Miller and Rohde had rediscovered a reaction first observed by Pasteur (70), namely, that the bitertiary bases cinchonine and quinine were converted under acidic conditions into ketones, designated as toxines, which contained a secondary amine function, and in order to explain these observations, made the fruitful suggestion that the non-aromatic moiety of the alkaloid molecules contained a bicyclic system with nitrogen at the



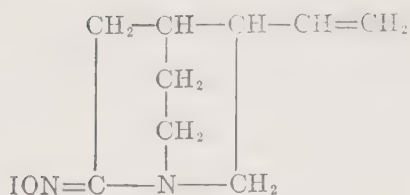
bridgehead, as in XVIII ($n = 0$ or 1) (71). Thus, the toxins were represented by the structure (XIX). Koenigs accepted this view (72), and pointed out that it was consistent with the formulation of cinchene and quinene as alkylidene lepidines (XX, $R = H$ or OCH_3); the latter expressions, which are now known to be correct, were in accord with the smooth hydrolytic cleavage of the anhydro bases to lepidines and



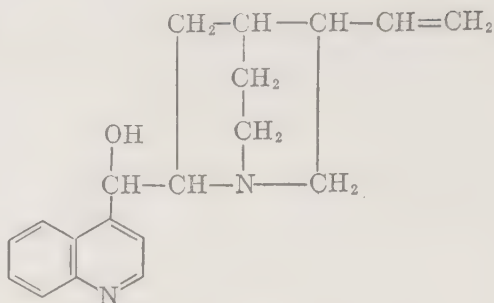
meroquinene (73). The first strong evidence that the oxygen atom of the cinchona toxins, and thence presumably that of the alkaloids themselves, was not attached to a carbon atom penultimate to the aromatic ring was forthcoming when Rabe showed that the α -isonitrosotoxines were best formulated as XXI, since they were converted under the conditions of the Beckmann rearrangement to quinoline-4-carboxylic acids and meroquinene nitrile (74). Then, the widely held view that the alkaloids were tertiary alcohols was doomed when Rabe succeeded



in oxidizing cinchonine directly to a ketone (75). Further, the structure of this ketone, cinchoninone (XXII), was demonstrated through cleavage by amyl nitrite and sodium ethoxide to cinchoninic acid (V) and an oximino compound (XXIII) which was hydrolyzed to meroquinene and hydroxylamine. Finally, it was possible to effect the



XXIII



XXIV

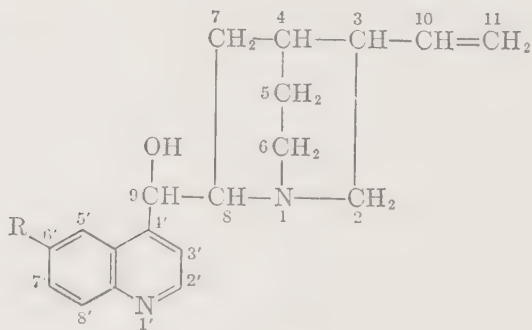
reconversion of cinchoninone, albeit in small yield, into cinchonine by reduction. These experiments showed conclusively that cinchonine possessed the structure XXIV.

The objective of the intensive structural investigations of more than a quarter of a century had been reached.

II. Reactions of the Alkaloids

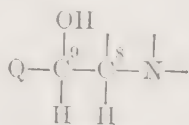
1. THE C.8-C.9 SYSTEM

We may turn now to a general consideration of the chemistry of the major cinchona alkaloids, in terms of the established structures, (XXV, R = H) for cinchonine and cinchonidine, and (XXV, R = OCH₃) for quinine and quinidine.



XXV.

The major transformations undergone by the alkaloids devolve from the presence in the bases of the ethanolamine system (XXVI, Q = 4-quinolyl or 6-methoxy-4-quinolyl).



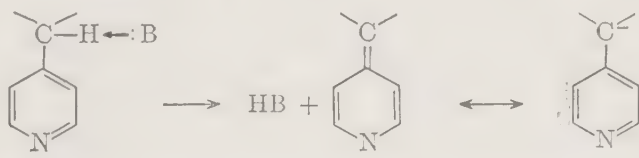
XXVI

We shall direct attention first to the special properties conferred on the system by its attachment at the γ -position of a quinoline nucleus. Any

$\text{---}\overset{\textstyle |}{\underset{\textstyle |}{\text{C}}}=\overset{\textstyle |}{\underset{\textstyle |}{\text{N}}}$ double bond, in consequence of the presence of the strongly electron-attracting nitrogen atom as a bond partner, is polarized in the sense $\text{---}\overset{\textstyle |}{\underset{\textstyle |}{\text{C}}}=\overset{\textstyle |}{\underset{\textstyle |}{\text{N}}}$, and will stabilize directly attached anionoid centers (*cf.* XXVIIa \leftrightarrow XXVIIb). Thus a hydrogen atom α to such a group will be relatively easily removed by basic reagents, and the resulting anion may undergo the manifold reactions characteristic of such centers. These

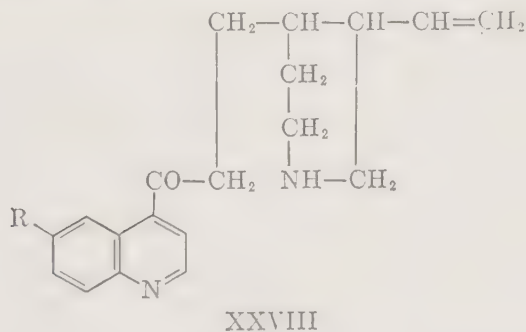


characteristics of the carbon-nitrogen double bond may be transmitted through a series of attached double bonds, and thus to selected positions of an aromatic heterocyclic nucleus. The well-known reactivity of the methyl and methylene groups attached in the α and γ positions of pyridine and quinoline nuclei is explicable in these terms. It is clear then, that the attachment of C.9 of the cinchona bases to the γ -position



of a quinoline ring provides the key to an understanding of a large portion of the chemistry of the alkaloids.

a. The Cinchona Toxines. One of the oldest and best-known reactions of the alkaloids is the conversion to the cinchona toxines, (70, 71, 77-79) cinchotoxine (XXVIII, R = H) and quinotoxine (XXVIII,

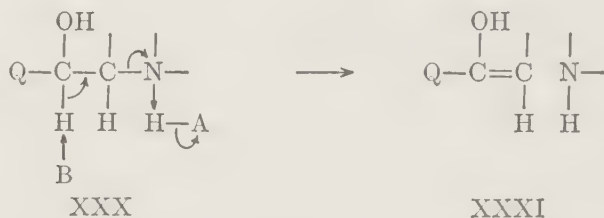


R = OCH₃). It may be noted that quinine and quinidine are converted to the same ketone, as are cinchonine and cinchonidine.

The considerations advanced above indicate that the C.9 hydrogen atom is susceptible to removal by bases; in the resulting fragment, the opportunity exists for the elimination of N (XXIX, arrows).

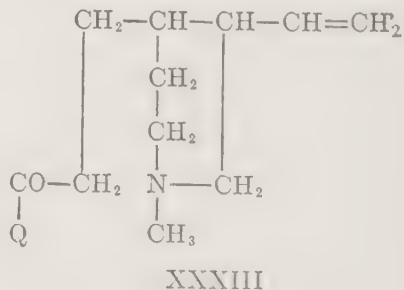
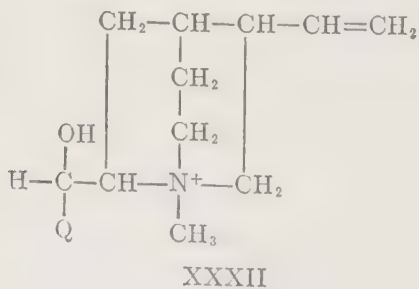


This process, however, will not be a ready one in the absence of factors which facilitate electron-accession to nitrogen. The most readily attainable such situation is the conference of a full positive charge on the nitrogen atom by salt formation. It is for this reason that the rate of toxine formation passes through a maximum as the acidity of the medium in which the change is brought about increases, and then decreases at higher acidities, as the suppression of loss of the C.9 hydrogen atom becomes dominant. For the overall reaction we may write a concerted process (XXX \rightarrow XXXI) in which cooperation of acidic and basic catalysts is essential (80).

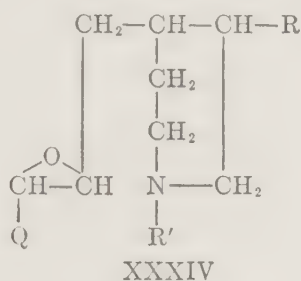


The transformation of the enol to the observed ketonic product is unexceptional.

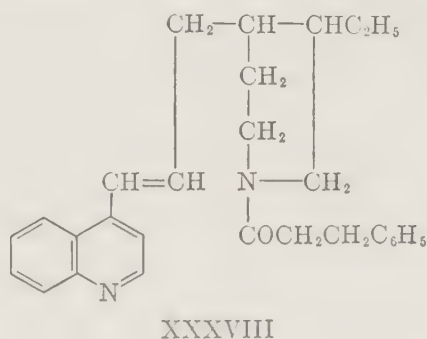
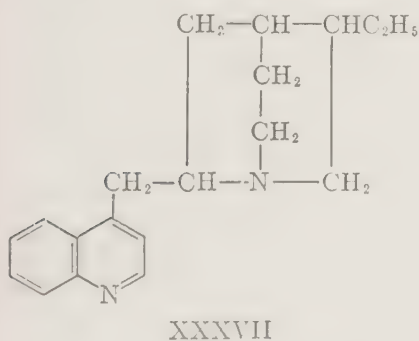
This view of the nature of the process is confirmed by the behavior of the quaternary salts (XXXII) derived from the alkaloids (81-87). These substances very readily undergo transformation to *N*-alkyl toxins (XXXIII) in the presence of *bases* alone. In these cases, a full positive charge is fixed on the nitrogen atom, and the base-catalyzed removal of H-C.9 alone initiates reaction. It is of interest that base-



induced toxine formation from the quaternary derivatives is frequently accompanied by the formation of oxides (XXXIV), through the sequence (XXXV \rightarrow XXXVI).



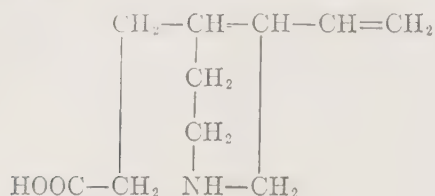
It may be noted that desoxydihydrocinchonine (XXXVII), when boiled with anhydrous hydrocinnamic acid furnishes XXXVIII, through changes essentially similar to those outlined above (88).



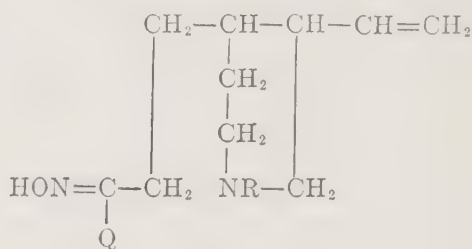
The reactions of the cinchona toxines are in general those to be expected of substances containing the structural features known to be present. The ready formation of α -isonitroso derivatives (XXI), and the cleavage of the latter to cinchoninic acid derivatives and meroquinene or its congeners has been mentioned in Section I. The interesting reactions which permit reconstitution of the cinchona alkaloid structure from the toxines are discussed in Section IV.

Of special interest are the methods which serve for the degradation of the ketones to derivatives of homomeroquinene (XXXIX). The Beckmann rearrangement of the toxine oximes (XL) proceeds in both

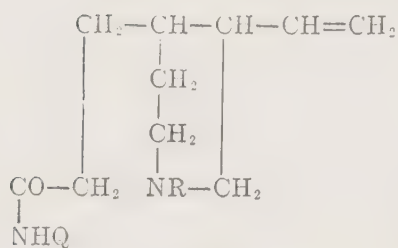
possible directions, to yield a mixture of the amides XLI and XLII (89, 90).



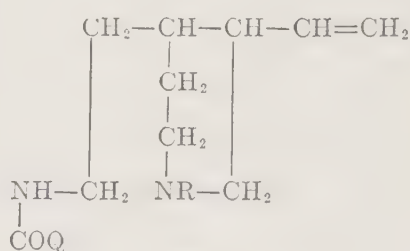
XXXIX



XL

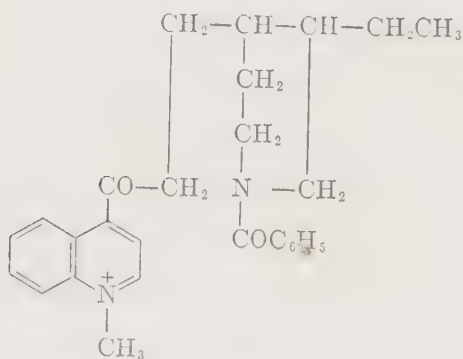


XLI

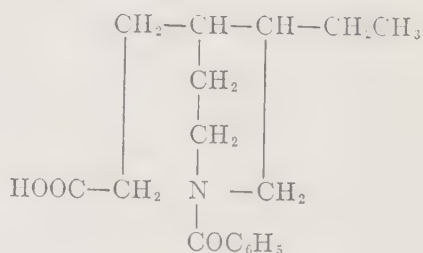


XLII

Direct oxidation of the ketones leads of course to the familiar cleavage between C.8 and C.9, but alkaline permanganate oxidation of *N*.1-benzoyldihydrocinchotoxine-*N*.1'-methiodide (XLIII) results in cleavage of the C.9-C.4' bond, with the formation of *N*-benzoylhomocincholipon (XLIV) (91).

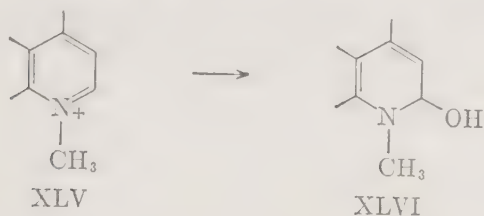


XLIII

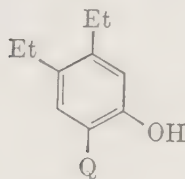
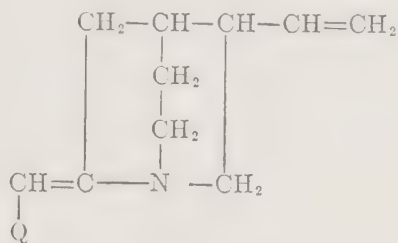


XLIV

The reaction sequence is explicable when it is realized that the aromatic ring, which is ordinarily very resistant to the attack of oxidizing agents, becomes very susceptible to oxidative degradation when the methiodide suffers the characteristic reaction of the class with hydroxide ions (XLV \rightarrow XLVI).

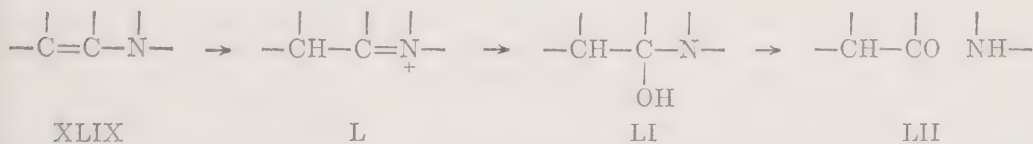


b. The Anhydro Bases. We have seen earlier that cinchene (XLVII, Q = 4-quinolyl) and quinene (XLVIII, Q = 6-methoxy-4-quinolyl) are produced when the corresponding cinchona chlorides are treated with alcoholic potash.



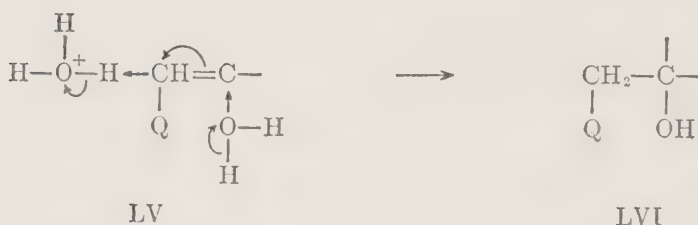
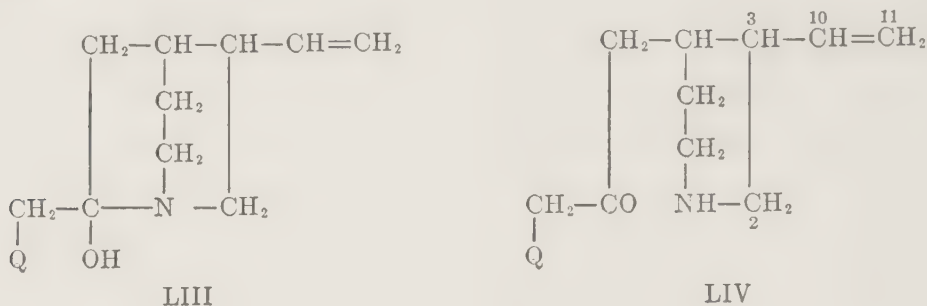
The action of acids on these anhydro bases brings about, on the one hand, cleavage to meroquinene and the corresponding lepidine, and on the other, a complicated reaction leading to the new bases, *apocinchene* and *apoquinene* (XLVIII) (13, 56, 58, 92, 93).

The cleavage reaction involves a point of special interest. Substances containing the system $\begin{array}{c} | & | & | \\ -C=C-N- \end{array}$ are ordinarily readily cleaved by aqueous acids, through the sequence (XLIX \rightarrow LII).

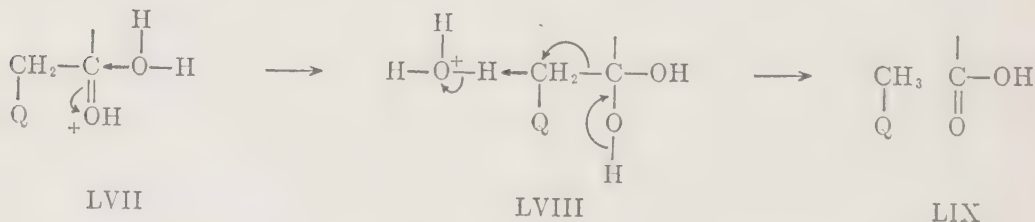


In the case at hand, however, the formation of a conjugate acid of the general class (L) is unlikely to be a major factor in the initiation of the

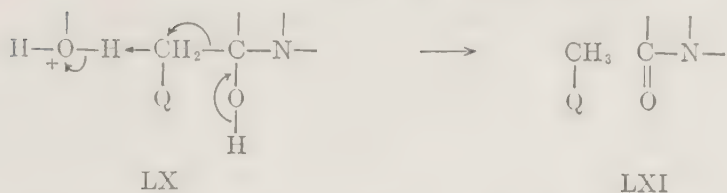
cleavage reaction, since a double bond at the bridgehead of the quinclidine system would be very highly strained. On the other hand, the $\Delta^{8,9}$ -double bond of the anhydro bases may in any event be directly hydrated to LIII in consequence of its attachment to the quinoline residue. The reaction sequence (*cf.* LV \rightarrow LVI) is essentially the reverse of the changes which occur in the conversion of the cinchona alkaloids to the toxins, and may be compared with the processes which permit the hydration of α,β -unsaturated ketones.



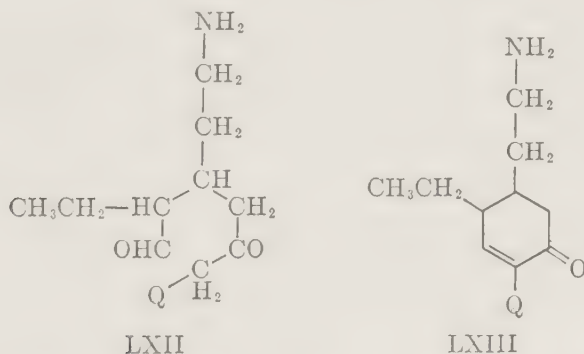
Now the intermediate LIII is simply a ring chain tautomer of LIV, which, like β -keto esters, β -diketones, and acyl picolines, may be cleaved to lepidine and meroquinene (*cf.* LVII \rightarrow LIX). Alternatively, LIII itself can suffer the very similar change (LX \rightarrow LXI). In the latter case,



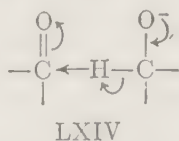
the cyclic amide of meroquinene which is the proximate product of the reaction may be expected to undergo very ready hydrolysis (*cf.* Section II, 1, c).



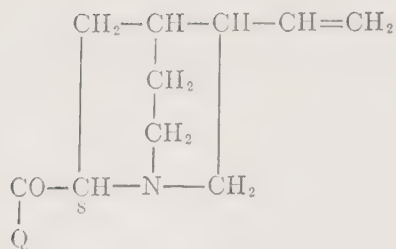
The formation from the anhydro bases of the *apo* compounds (XLVIII) is so complicated a change that its course cannot be specified in detail. However, it is probable that its first steps are related to the simpler reactions just discussed. It will be clear that any intermediate of the type LIV possesses a very reactive C.9 methylene group. Now, if at the same time that the changes outlined above are occurring, the $\Delta^{10,11}$ bond of the anhydro bases moves, by a series of simple acid catalyzed isomerizations, to $\Delta^{2,3}$, and is there cleaved (*cf.* XLIX \rightarrow LII), the resulting species (LXII), will undergo very ready internal condensation to LXIII. For the rest, the elimination of ammonia, and the movement of the resulting double bond to a position permitting aromatization, is required.



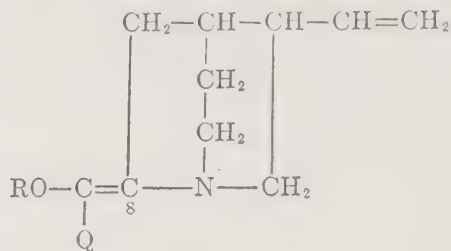
c. The Cinchona Ketones. The transformation of the cinchona alkaloids into the corresponding ketones is best effected by oxidation with benzophenone in the presence of potassium tertiary butoxide (94). The reaction involves hydride ion transfer (LXIV); it is similar to the Oppenauer oxidation, and may be of general applicability in instances in which



the use of aluminum alkoxides fails. The same reaction may be used for the reconversion of the ketones to the alcohols. Quinone (LXV), for example, is smoothly reduced to readily separable mixtures of quinine and quinidine by excess alkali secondary alkoxides.

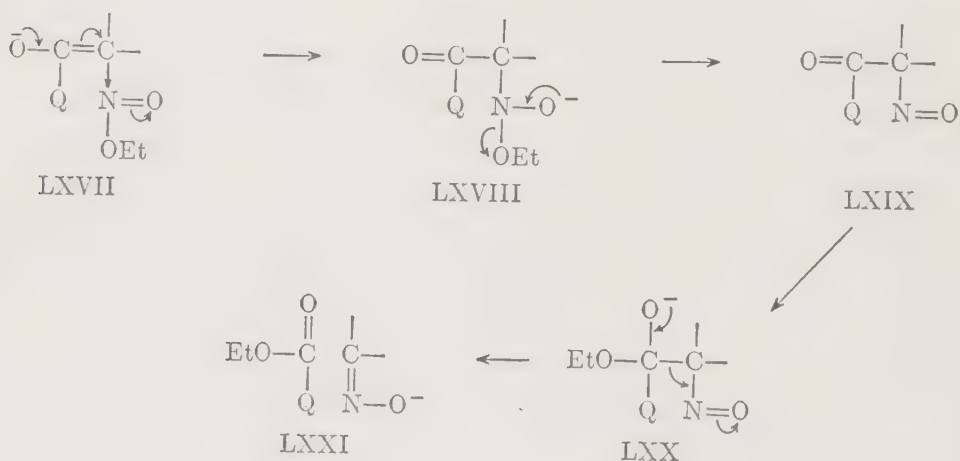


LXV

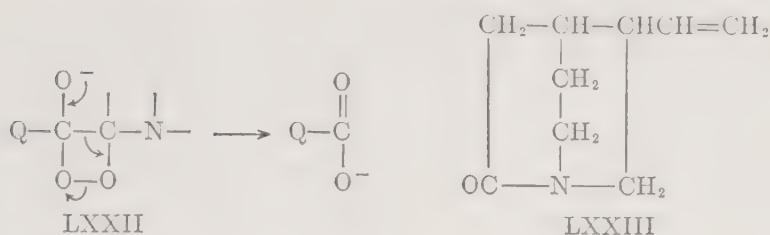


LXVI

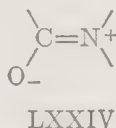
The cinchona ketones resemble α -diketones in that they enolize very readily. For this reason, freshly prepared solutions of the crystalline ketones exhibit the phenomenon of mutarotation, as the ketone of one configuration is converted, through the enol, to an equilibrium mixture of C.8 epimers. Enol derivatives, such as the benzoyl (LXVI, $\text{R} = \text{C}_6\text{H}_5\text{CO}$) and toluenesulfonyl (LXVI, $\text{R} = \text{C}_7\text{H}_7\text{SO}_2$) esters are readily prepared. The cleavage of the ketones by sodium ethoxide and alkyl nitrites (95) has already been mentioned (Section I); here we may point out that the reaction involves the attack of the anion of the enol (LXVI, $\text{R} = \text{H}$) on the nitrite, followed by a cleavage reaction (LXVII \rightarrow LXXI) similar to that which is familiar in the cases of β -diketones and β -keto esters.



Finally, mention may be made of the high susceptibility of the alkali enolates to attack by oxygen (96). In the presence of potassium tertiary butoxide, quinone reacts smoothly with one mole of oxygen, to give potassium quinate, and the tertiary butyl ester of meroquinone. The reaction very probably involves the formation of an unstable cyclic peroxide (LXXII), which decomposes as shown to the salt of quininic

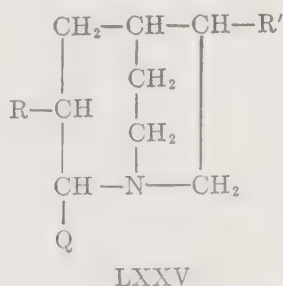


acid and the lactam (LXXIII) of meroquinene. The observed phenomena suggest that the lactam (LXXIII) is unusually reactive, a circumstance which may be considered surprising until it is realized that the special environment of the amide link in (LXXIII) may be expected to confer unusual properties on the function. Thus, the amide link is ordinarily stabilized by resonance involving a dipolar contributor (LXXIV). Concomitant with this internal electron-distribution is a marked lowering of the normal additive capacity of the carbonyl group.



Now in LXXIII, stabilization through participation of dipolar contributors such as LXXIV will be minimized, or absent, since the geometry of the bicyclic system is incompatible with the requirement, for maximum acceptance by a given bond of partial double bond character, that the groups attached to the bond partners must lie in or near a common plane. Consequently the carbonyl group of LXXIII retains much of the reactivity of the normal carbonyl function, and the amide linkage is readily cleaved.

d. The Hetero Bases (97). When the cinchona alkaloids are converted to the corresponding halides by the action of phosphorus halides, isomeric substances (LXXV, $\text{R} = \text{Hal}$; $\text{R}' = \text{Et}$ or C_2H_5) known as *hetero* bases are also formed in small quantity.



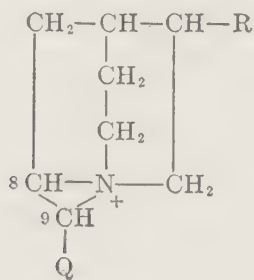
Benzoates (LXXV, $\text{R} = \text{C}_6\text{H}_5\text{COO}$) of the *hetero* series are formed when the tosyl derivatives of cinchonine and hydrocinchonine are treated with

potassium benzoate in ethanol (98–100). Finally, the normal and *epi* cinchona bromides (*cf.* Section III) are converted to *hetero* ethers (LXXV, R = OMe or OEt) by treatment with silver benzoate or silver carbonate in methanol or ethanol. The reverse reaction occurs when *hetero* hydrocinchonine bromide (LXXV, R = Br) is treated with silver benzoate in dry acetone; a mixture of the benzoates of hydrocinchonine and *hetero* hydrocinchonine is obtained.

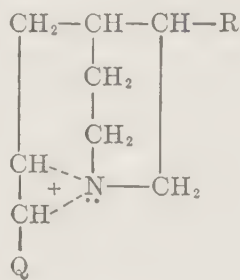
The compounds of the *hetero* series are remarkable for their relatively low basicity. It may be suggested that the attainment of tetrahedral character by the nitrogen atom on acquisition of a proton is opposed relatively strongly in the 1-aza-[2,3,3]-bicyclononane system present in the *hetero* bases.

The failure of the *hetero* alkaloids (LXXV, R = OH) to undergo transformation to toxins is attributable to the absence of activation of the C-H bond whose scission would be essential for the change (*cf.* II, 1, *a*).

All of the modes of rearrangement of the normal into the *hetero* compounds indicate that the first step in the reactions is a direct or induced ionization of a strongly electronegative group (Br, OTs, or OPX₄). The most obvious mode of stabilization of the resulting cation is through formation of a cyclic ammonium derivative (LXXVI); in this case, the rearrangements would be directly comparable to those of



LXXVI



LXXVII

many 1,2-halo amines, and attack at C.8 or C.9 could lead to substances of the *hetero* or normal series, respectively. On the other hand, an intermediate (LXXVI) may be expected to be very highly strained, and the possibility should be considered seriously that the reaction is more nearly comparable to a simple Wagner-Meerwein shift, with formation of a three-center intermediate involving C.8, C.9 and the electron pair of the original C.8-N bond (LXXVII) as ionization proceeds.

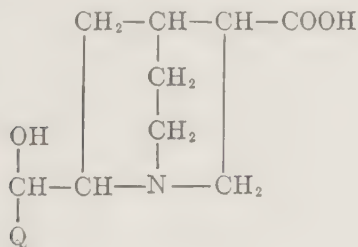
Hetero quinine has been shown to be present in very small amounts in commercial quinine (101).

2. REACTIONS PRIMARILY INVOLVING THE VINYL GROUP

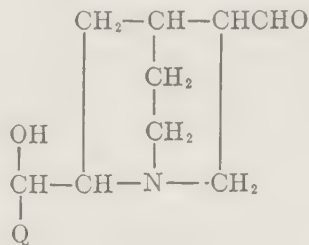


a. Simple Addition and Cleavage Reactions. The addition of hydrogen, halogen acids (14-22), halogens (12, 14, 22, 23), and other reagents to the vinyl group of the cinchona alkaloids in general proceeds normally, and more or less smoothly. Here we shall only call attention to the fact that the more negative fragment of unsymmetrical addends appears, as expected, at C.10, and that the creation of asymmetry at this center permits *a priori* the formation of two stereoisomers, which are often found, in a given addition reaction (102).

The oxidative cleavage of the vinyl group to acids, known as *tenines*, for example, cinchotenine and quitenine (LXXVIII), has already been mentioned (Section I). Ozonization of the alkaloids gives the expected aldehydes (LXXIX) (103).

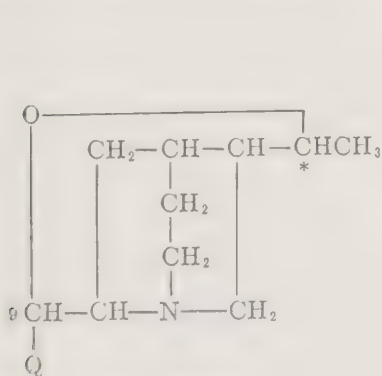


LXXVIII

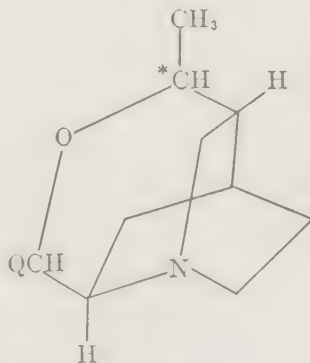


LXXIX

Of special interest is the cooperation of the hydroxyl and vinyl groups in the formation of seven-membered cyclic ethers. Among the products formed by the action of acidic reagents on cinchonine are α -isocinchonine and β -isocinchonine (LXXX \equiv LXXXI) (104-108). These substances differ only in configuration at C.10 (starred), and their

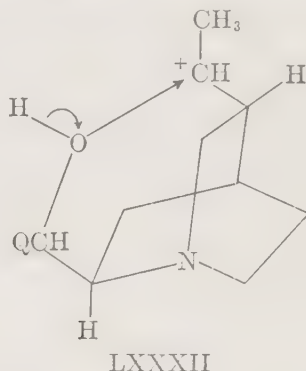


LXXX



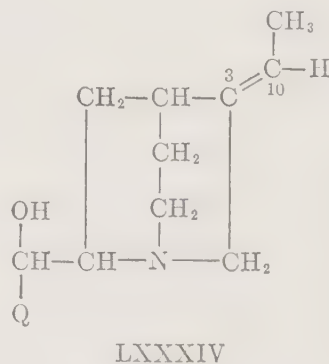
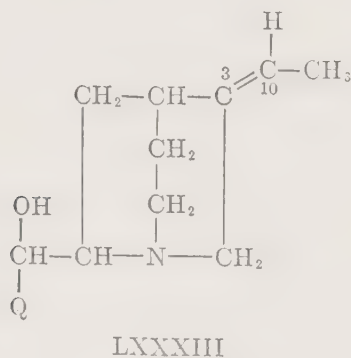
LXXXI

formation may well be the result of a concerted process, in which C.10 becomes cationoid and is attacked directly by the hydroxyl group (LXXXII, arrows). From quinidine, the preparation of three substances, the α -, β -, and γ -isoquinidines (108–113), which appear to be



cyclic ethers of the formula LXXXI, has been reported. The existence of three such isomers may be attributable to inversion at C.9 in the formation of one of the substances, but the possibility of more deep-seated changes has not been rigorously excluded. It is noteworthy that the formation of similar ethers from quinine and cinchonidine is sterically impossible (cf. Section III).

b. Migration of the Double Bond. The action of hot mineral acids on the cinchona alkaloids readily brings about isomerization of the double bond to the $\Delta^{3(10)}$ position. Geometrical isomerism is possible in the products, and in many cases, the two possible forms, (LXXXIII) and (LXXXIV), are known. The same compounds are formed, along with other substances, when the hydrogen halide addition products of the alkaloids are treated with bases.

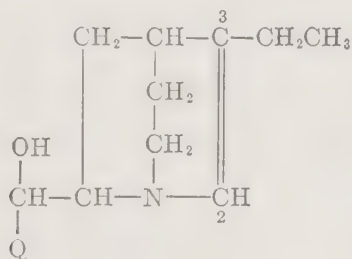


Thus, from cinchonine, *apocinchonine* is formed (104, 107), while cinchonidine yields the isomeric pair, *apocinchonidine* (114) and β -cinchonidine (115, 116). Correspondingly, in the quinine series the $\Delta^{3(10)}$

bases are represented by α -isoquinine (112, 117) and β -isoquinine (112, 118) while quinidine leads to *apo*quinidine methyl ether (112) and *neois*quinidine (112).

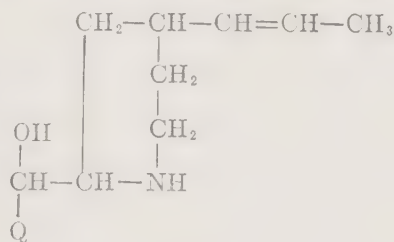
The double bond in these substances is readily hydrogenated, with the formation of mixtures of the corresponding dihydrocinchona alkaloids, and isomeric dihydro-bases which differ in configuration at C.3 (*cf.* Section III, 1). Ozonization of the $\Delta^{3(10)}$ -bases proceeds abnormally, and leads to 3-acetyl derivatives (119).

In the quinidine series, a third unsaturated base, ψ -quinidine (112), is known, which is hydrogenated to the same mixture of dihydro bases as that obtained from *apo*quinidine methyl ether and *neois*quinidine. It is possible that in ψ -quinidine, the movement of the double bond has proceeded another stage, with the formation of the $\Delta^{2,3}$ isomer (LXXXV).



LXXXV

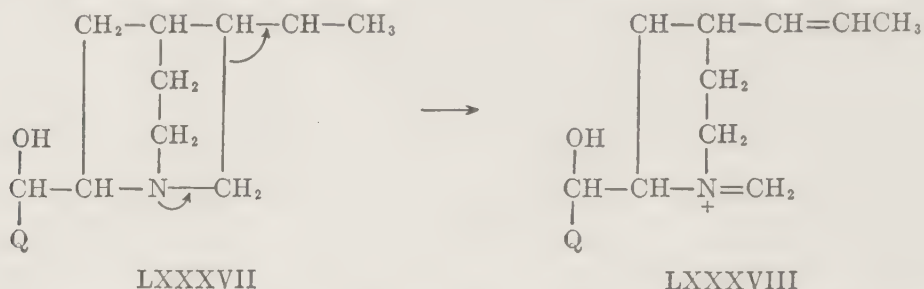
c. Formation of the Niquine Bases. When the products formed by the addition of hydrogen halides to the vinyl group of the cinchona alkaloids are treated with alkalies, or with silver salts, they are transformed in part to new bases, the niquines (LXXXVI), with loss of C.2 as formaldehyde (107, 109, 120-125).



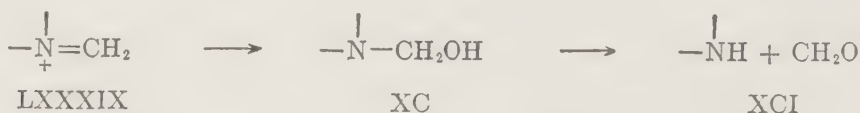
LXXXVI

From quinine, niquine is obtained in this way. As in the case of the $\Delta^{3(10)}$ bases, geometrical isomerism about the double bond in LXXXVI is possible, and is observed. Thus, from quinidine, niquidine and isoniquidine are obtained, and may be hydrogenated to the same base, dihydroniquidine. The type is probably represented in the cinchonine series by the α - and β -cinchonhydrines.

The processes which lead most smoothly to the niquine bases are those which may be considered most effective in generating a cationoid center at C.10. This fact provides a clew to the mechanism of the change, which undoubtedly involves the satisfaction of electron deficiency at C.10 through the displacements shown in LXXXVII (arrows) (126).



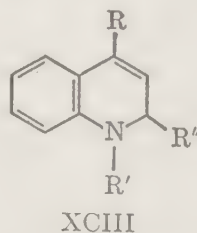
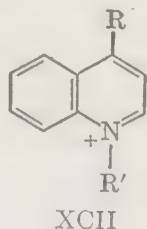
The loss of formaldehyde through the subsequent processes (LXXXIX \rightarrow XCI) is unexceptional.



3. MISCELLANEOUS TRANSFORMATIONS

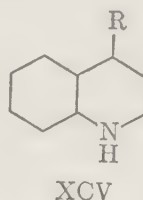
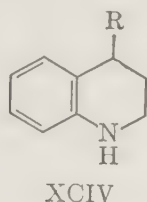
a. Demethylation. The demethylation of quinine to the naturally occurring phenolic base cupreine (XXV, R = OH) cannot be brought about under acidic conditions, since changes involving the vinyl group occur simultaneously (118, 127, 128). Conversely, partial demethylation is often a complicating factor in the acid-catalyzed isomerizations of the methoxy bases.

b. Reactions of the Pyridine and Quinoline Rings. The action of alkyl iodides on the cinchona alkaloids ordinarily takes place at the more basic quinuclidine nitrogen atom. On the other hand, yellow *N*.1'-alkyl iodides may be prepared by the action of alkyl iodides on the alkaloid hydroiodides in sealed tubes. The latter (XCII) are converted by Grignard reagents to 2-alkyl-1,2-dihydroquinolines (XCIII) (129).

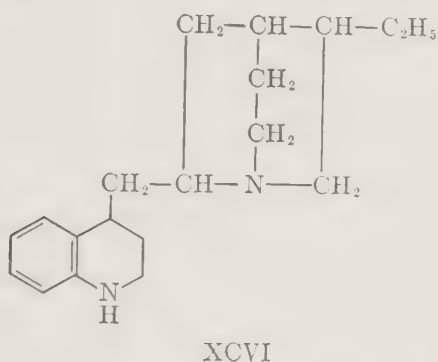


Phenyllithium attacks the 2' position of dihydrocinchonine directly, to give 2'-phenyldihydrocinchonine (130).

Hexahydrocinchonine (XCIV) and dodecahydrocinchonine (XCV) have been prepared by vigorous catalytic hydrogenation of cinchonine (131).

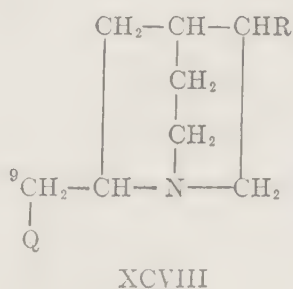
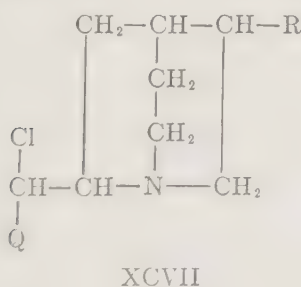


When dihydrocinchonine is reduced with sodium and amyl alcohol, simultaneous reduction of the pyridine ring and removal of the hydroxyl group at C.9 take place, with the formation of hexahydrodesoxycinchonine (XCVI) (132).



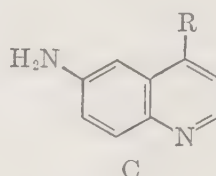
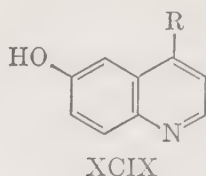
A considerable number of 5'-substituted, and 5', 8'-disubstituted derivatives of the methoxylated alkaloids has been prepared by direct substitution reactions (133).

c. Formation and Reactions of the Desoxy Bases. The desoxy bases, of the general structure XCVIII, have usually been prepared by transformation of the cinchona alkaloids into chlorides (XCVII) by phosphorus pentachloride and removal of the halogen in the latter by metal-acid combinations (64, 97, 134, 135, 136). It is reported that direct removal of the hydroxyl group is brought about by electrolytic reduction (132).



The desoxy compounds, like other similarly constituted substances, (*cf.* α - and γ -picoline) condense with formaldehyde at C.9 (137). The significance of the compounds in connection with the stereochemistry of the cinchona alkaloids is discussed in Section III.

d. Removal of the Oxygen Atom at C.6'. Dihydroquinidine has been demethylated to dihydrocupreidine (XCIX). Conversion of the phenolic base to the corresponding amine (C) by the Bucherer reaction, followed



by diazotization and reduction by hypophosphorous acid, led to dihydrocinchonine (138). In a similar way, cupreine was converted to cinchonidine. These transformations proved rigorously the long-assumed relationships, 6'-methoxycinchonine = quinidine, and 6'-methoxycinchonidine = quinine.

e. Reactions at N.1. Numerous halides react with the cinchona alkaloids at N.1 to give quaternary salts (139). Perbenzoic acid, or hydrogen peroxide, converts quinine and cinchonine smoothly to the corresponding N.1-oxides (140-142). It is of some interest that the vinyl group in quinine N.1-oxide can be hydrogenated without disturbance of the oxide function (140).

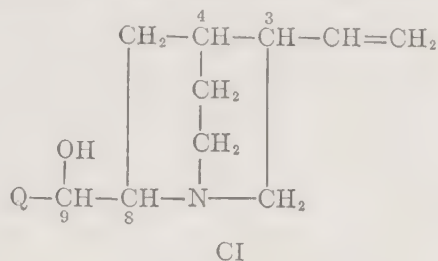
f. Metabolic Reactions. Animal tissues appear to contain an enzyme system which catalyzes the oxidation of the cinchona alkaloids. A number of oxidation products is formed of which the 2'-hydroxy derivatives of quinine and cinchonine have been isolated and identified (143, 144).

III. Stereochemistry

The first work on the stereochemistry and optical properties of the cinchona bases was undertaken by Pasteur (70, 145) in 1852. In the course of these investigations Pasteur achieved one of the greatest initial triumphs of stereochemistry, by showing that racemic acids could be resolved through combination with asymmetric alkaloidal bases. He also made the observation, which was to be of fundamental importance in studies on the structure, stereochemistry, and synthesis of the cinchona alkaloids, that the bases were convertible to isomeric substances, now known as toxines, and first classified the natural alkaloids on the basis of their optical properties. Thus, at this early date, the stereochemical relationship of the dextro rotatory substances, quinidine and cinchonine,

on the one hand, and the laevo rotatory bases, quinine and cinchonidine, on the other, was foreshadowed.

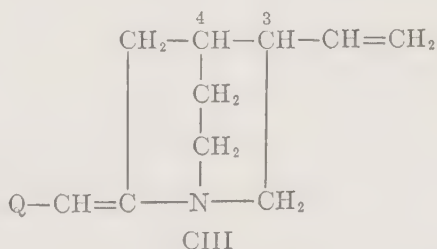
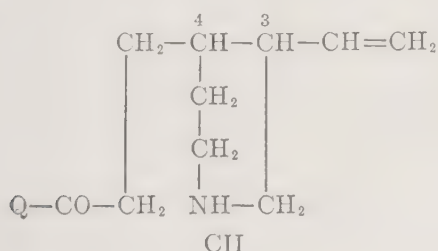
It is now known that each of the major natural alkaloids (CI) possesses four asymmetric centers (C.3, C.4, C.8, C.9).



In the sequel, the configurational evidence relating to each of these centers will be discussed in turn.

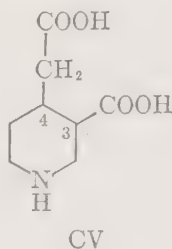
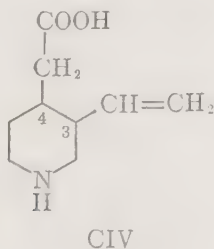
1. C.3 AND C.4

Cinchonine and cinchonidine are convertible into the same substance, cinchotoxine (CII) (71, 146), in which asymmetry at C.8 and C.9 is no longer present. The two alkaloids therefore possess identical configurations at C.3 and C.4. The comparable transformations of quinine and quinidine to quinotoxine permit a similar conclusion for this pair (77, 114).



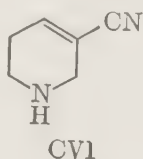
The same conclusion is reached through consideration of the formation of the anhydro bases; cinchonine and cinchonidine give the same cinchene (CIII), while quinene is obtained from both quinine and quinidine (*cf.* Section II, 1, *b*).

Since all four alkaloids can be degraded to meroquinene (58, 59, 72, 95) (CIV) by methods which do not involve inversion at C.3 or C.4, the



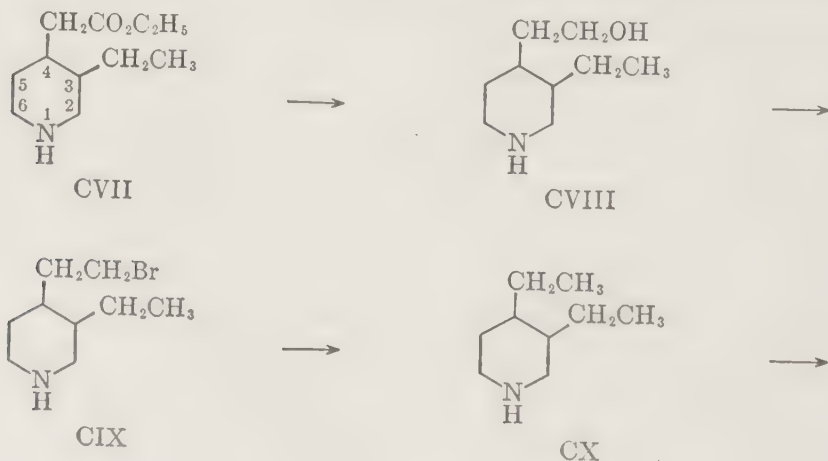
further conclusion may be drawn that *all of the substances possess identical configurations at these centers.*

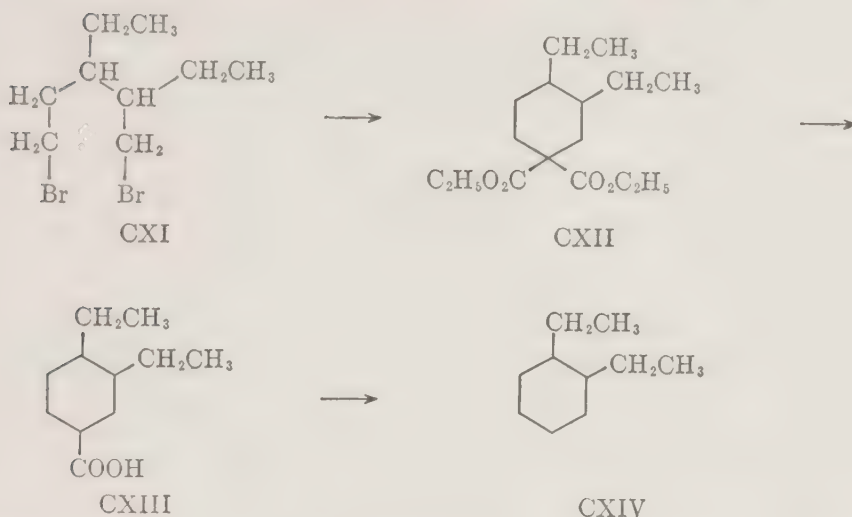
From the alkaloids, by more extensive degradation (60, 147), or from meroquinene (64, 148), *d*- β -cincholoiponic acid (CV) is obtainable. This acid is unstable with respect to a stereoisomer, *d*- α -cincholoiponic acid, into which it is transformed when it is heated with aqueous potash (65). This result suggests that the β -acid, and thence, the alkaloids themselves, possess the *cis* orientation of the groups attached to the piperidine ring. The conclusion is strengthened by consideration of the synthesis of the α - and β -cincholoiponic acids (*cf.* Section IV, 2). When malonic ester was added to the nitrile CVI, a reaction mixture was obtained from



which, by hydrolysis and decarboxylation, *dl*- β -cincholoiponic acid was formed in much smaller amount than the *dl*- α -acid (68, 69). It is clear that the predominant product of the reaction may be assigned the *trans* configuration with some confidence.

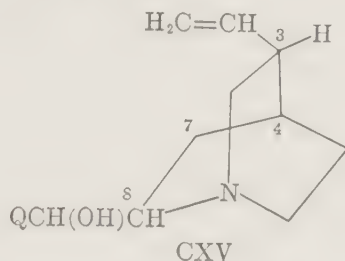
Conclusive evidence for the *cis* arrangement at C.3 and C.4 was provided by Prelog and Zalán (149). These investigators reduced cinchonine to dihydrocinchonine and converted the product by the procedure of Kaufmann, Rothlin and Brunschweiler (91) into cincholoipon ethyl ester (CVII), in which C.3 and C.4 retain the original configuration of cinchonine. Reduction of (CVII) with sodium and alcohol afforded 3-ethyl-4-(β -hydroxyethyl)-piperidine (CVIII), which with hydrobromic acid furnished the hydrobromide of 3-ethyl-4-(β -bromoethyl)-piperidine (CIX). The latter substance was converted by zinc and acetic acid into





3,4-diethylpiperidine (CX), which on von Braun degradation yielded the dibromo derivative (CXI). The dibromide was then coupled with malonic ester, and saponification and decarboxylation of the resulting dicarboxylic ester (CXII) afforded optically *active* diethylcyclohexanecarboxylic acid (CXIII). Treatment of the silver salt of the latter product with bromine gave 1-bromo-3,4-diethylcyclohexane, which on reductive debromination (Raney nickel) yielded optically *inactive* diethylcyclohexane (CXIV). The optical results provide conclusive evidence for a *cis* arrangement of the two ethyl groups in the diethylcyclohexane, and since none of the steps employed in the conversion of cinchonine into (CXIV) involves the asymmetric centers at C.3 and at C.4, the vinyl group of the natural cinchona bases must be *cis* to the C.7-C.8 bridge in all of the alkaloids.

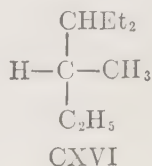
We are now justified in assigning to the cinchona bases, the partial stereochemical structure (CXV).



Of further interest is the conversion of the bromide (CXI) to (–) 3-methyl-4-ethylhexane (CXVI).^{*} The degradation of cinchonine to

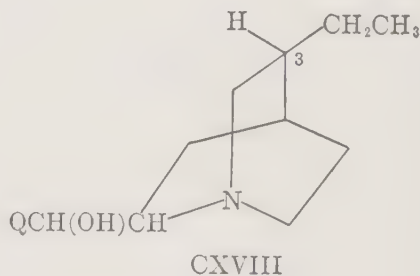
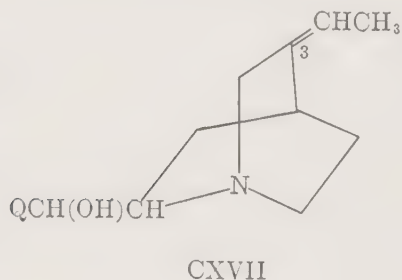
^{*} This formula, as well as the later expressions CXXVII through CXXX (cf. Section III, 3) are drawn according to the Fischer convention (*Ber.*, **24**, 2683 (1891)). The horizontal lines project forward, and the vertical ones, backward.

this simple reference substance containing only one asymmetric carbon atom makes possible the correlation of the absolute configuration at C.3 of the cinchona alkaloids with that of asymmetric centers in other natural



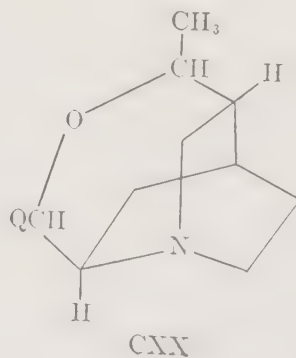
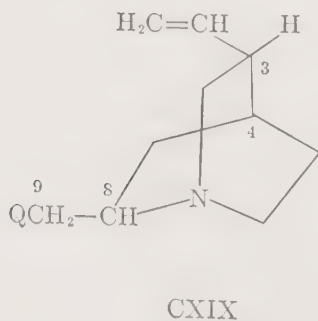
substances (150). It also forms the basis for the particular space formulae used throughout our discussion. Should it become necessary to reverse the present conventions with regard to absolute configuration, each of our representations should be replaced by the corresponding mirror image.

It may be mentioned that 3-*epi* dihydro bases (CXVIII) are formed along with the normal dihydroalkaloids by the catalytic hydrogenation of $\Delta^{3(10)}$ bases (CXVII) (*cf.* Section II, 2, *b*) such as α - and β -isoquinine, and apoquinidine methyl ether (112).



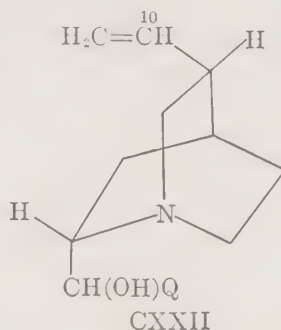
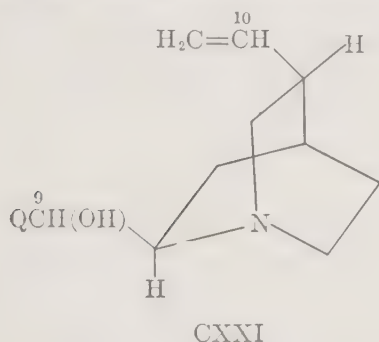
2. C.8

When the hydroxyl group at C.9 of cinchonine is removed, a desoxy base (CXIX) is obtained, which is isomeric with that derived in a similar fashion from cinchonidine (134, 151).

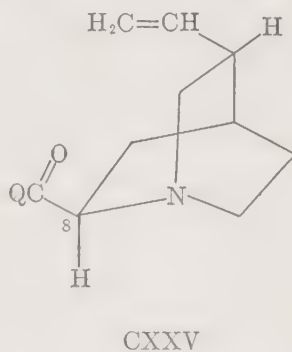
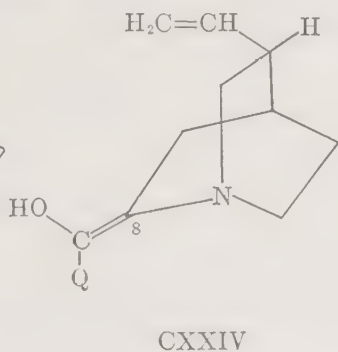
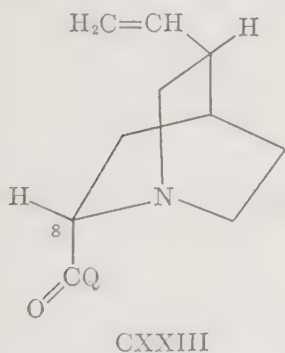


Since the configurations at C.3 and C.4 in the alkaloids are identical, these results require that the desoxy bases and hence, their progenitors, differ in the arrangement of groups about C.8. Quinine and quinidine are similarly related.

The assignment of configurations at C.8 may be deduced from the circumstance that cinchonine and quinidine are convertible into cyclic ethers (CXX) (*cf.* Section II, 2, *a*). No similar changes can be brought about with quinine and cinchonidine. Since ether formation is possible only when the C.8-C.9 and the C.3-C.10 bonds are in the *cis* relationship, we may assign the structures CXXI to cinchonine and quinidine, and CXXII to cinchonidine and quinine (152).



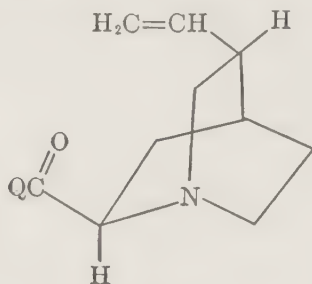
It might be expected that oxidation of cinchonine and of cinchonidine would furnish epimeric 9-keto compounds. Both substances, however, yield the same crystalline ketone, cinchonidinone* (CXXIII) (75, 153).



Quinidinone* is similarly obtained by oxidation of quinine or quinidine (94, 153). These results are attributable to the fact that the primary oxidation products, for example, cinchoninone (CXXV) from cinchonine, and cinchonidinone (CXXIII) from cinchonidine, possess an asymmetric center (C.8) adjacent to a carbonyl group, and are therefore capable of

* The inappropriate names, cinchoninone and quininone are used for these substances in the literature. Evidence in support of the present nomenclature follows.

equilibration through the common enol (CXXIV) (135, 153). The fact that only one ketone can be isolated from equilibrium mixtures is probably a consequence of its lesser solubility. The cinchona ketones afford enol derivatives with great ease (76, 94), and freshly prepared solutions of cinchonidinone mutarotate, the change being in the direction of greater dextrorotation (135). The mutarotation of quinidinone (CXXVI), on the other hand, is in the opposite direction. In the latter case, the sign of the rotational change (negative) is that expected for a transformation



CXXVI

from the quinidine to the quinine configuration, since desoxyquinidine has a much higher positive rotation ($+211^\circ$) than does desoxyquinine (-98°). Application of similar reasoning to the positive mutarotation of cinchonidinone leads to the conclusion that the change is from the cinchonidine to the cinchonine configuration, since desoxycinchonidine is laevorotatory (-30°) whereas desoxycinchonine shows a high positive rotation ($+179^\circ$). Supporting chemical evidence for these assignments is available in the observation that hydrogenation of a freshly prepared solution of dihydroquinidinone gives predominantly dihydroquinidine (94) and 9-*epidi*hydroquinidine. Hydrogenation of aged solutions, on the other hand, gives in addition to these products, dihydroquinine and 9-*epidi*hydroquinine (97).

3. C.9

Since C.9 is not incorporated in a rigid system, the determination of configuration at this center represents a problem of greater difficulty than that encountered in connection with the other asymmetric centers.

For each configuration at C.8, two isomers are possible which differ in orientation at C.9. Since all of the alkaloids are identical in configuration except at C.8 and C.9, four isomeric substances are possible in each series. In one series two of these substances are represented by cinchonine and cinchonidine. The other two members are *epicinchonine* and *epicinchonidine*. Quinine, quinidine, *epiquinine* and *epiquinidine* constitute another such series. The normal members of these series are the major natural alkaloids. The *epi* compounds may occur naturally

in very small quantities, and are obtained as by-products in the reduction of the cinchona ketones (154, 155), by direct equilibration of the natural alkaloids through drastic treatment with alkalis (*cf.* Section III, 4), and by inversion reactions at C.9.

In most respects, cinchonine and cinchonidine parallel one another closely in their chemical behavior, and differ qualitatively from the isomeric pair, *epicinchonine* and *epicinchonidine*. Since cinchonine and cinchonidine differ in configuration at C.8, these facts suggest that the two alkaloids differ also in configuration at C.9, for only in these circumstances will similar geometric relationships obtain in the C.8-C.9 systems. On like grounds it may be surmised that quinine and quinidine also differ in configuration at C.9.

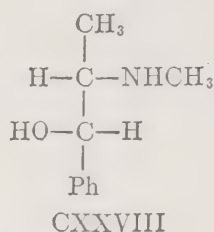
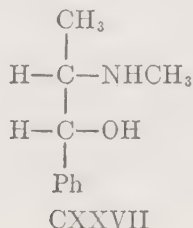
These conclusions are supported by consideration of optical data. The specific rotations of the four members of each series are as follows:

Cinchonine	+224°
<i>Epicinchonine</i>	+120°
<i>Epicinchonidine</i>	+ 63°
Cinchonidine	-111°
Quinidine	+254°
<i>Epiquinidine</i>	+102°
<i>Epiquinine</i>	+ 43°
Quinine	-158°

It is clear that the partial rotatory contributions both at C.8 and C.9 must be positive in the most strongly dextrorotatory substances, cinchonine and quinidine, and negative in the laevorotatory isomers, cinchonidine and quinine. From the principle of optical superposition, it follows that cinchonine and cinchonidine, like quinine and quinidine, possess different configurations at C.9. It may be noted further that these relations first formed the basis for the recognition, since established by direct chemical interconversions (*cf.* Section II, 3, *d*), that quinine is methoxycinchonidine, and quinidine, methoxycinchonine. In this general connection, it should be pointed out that exceptionally complete optical information is available for the cinchona alkaloids and their derivatives, and that this data has not infrequently been of value in providing intimations of stereochemical relationships, the correctness of which has subsequently been rigorously demonstrated by chemical means. The optical superposition rule is not quantitatively obeyed, but qualitative agreement is good, with certain notable exceptions (for example, the cinchona bromides).

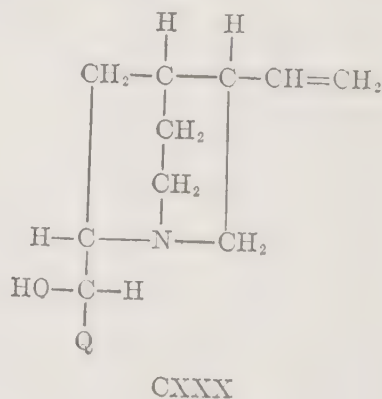
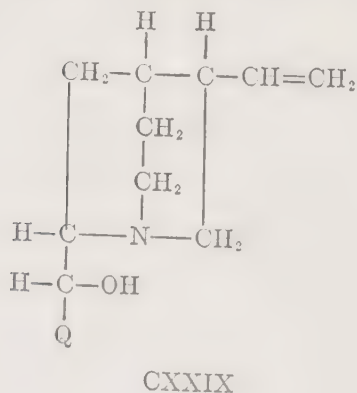
We turn now to a consideration of the actual orientations at C.9 in the cinchona bases. Of the arguments which may be presented (156, 157), that which correlates the alkaloids with (-) ephedrine (CXXVII) and (+) ψ -ephedrine (CXXVIII) (158-161) appears to us the sounder,

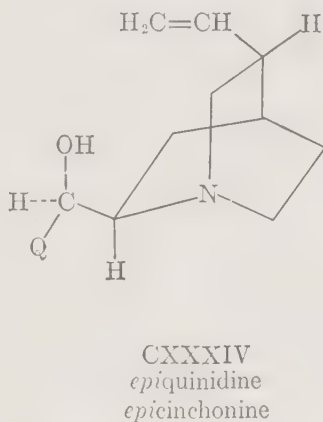
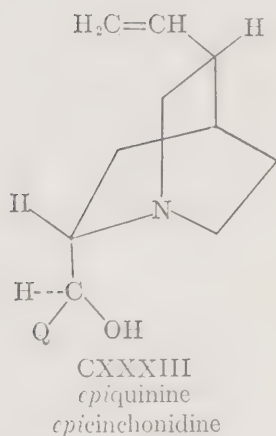
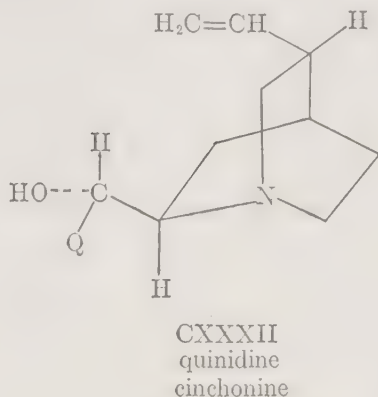
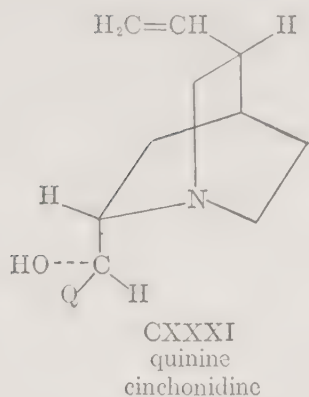
and forms the basis of the present discussion. Of the formulae CXXIX and CXXX, one must represent quinine, and the other, *epi*quinine. In these expressions, as well as in those for the ephedrine, the configuration at each asymmetric atom is that given by the Fischer convention (*cf.* footnote, p. 27).



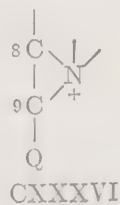
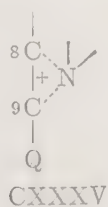
Now, *epi*quinine is a stronger base than quinine (97, 162), and ψ -ephedrine is more strongly basic than ephedrine (163). From this analogy, *epi*quinine may be assigned structure CXXX. It should be pointed out that this argument does not rest entirely on a purely formal basis. Inspection of models shows that the formation of a *quasi* ring involving —OH and —NR₂ in either ephedrine (CXXVII) or quinine (CXXIX) is strongly opposed, in the first case by interference between the bulky methyl and phenyl groups, and in the latter by similar repulsion between the quinoline and quinuclidine systems. On the other hand, in ψ -ephedrine (CXXVIII) and *epi*quinine (CXXX), the same steric factors favor a conformation in which —OH and —NR₂ are proximate in space. Prelog⁺ has suggested that when the —OH and —HNR₂ groups are suitably disposed, internal hydrogen bonding, possibly with the participation of one or more molecules of solvent, may stabilize the conjugate acid forms, and in this way, confer greater basicity on the corresponding bases. In accordance with this view, the *epi* compounds are in general more basic than the corresponding normal isomers.

It is now possible to write full structures (CXXXI, CXXXII, CXXXIII, CXXXIV) for each of the cinchona alkaloids.





The stereochemistry of reactions occurring at C.9 is of some interest. The *O*-toluenesulfonyl derivative of cinchonine is transformed by potassium benzoate into the benzoate of *heterocinchonine* (97–100). When the stereochemically similar quinidine *O*-toluenesulfonate is treated with aqueous potash, it is converted in part into quinidine, and in larger measure to an unidentified oily product (164); analogy, and the considerations outlined below suggest that the latter material may be a mixture of *heteroquinidine* and anhydro bases. On the other hand, when the tosylate is warmed with aqueous tartaric acid, *epiquinidine* is smoothly formed (164). It may be suggested that in the basic media ionization of the tosyl group leads to a cation of the type (CXXXV), or less probably (CXXXVI) (*cf.* Section II, 1, *d*). Attack of the anion (OH^- or OBz^-)



may now occur either at C.8 with the formation of a *hetero* derivative, or at C.9 *with retention of configuration*. On the other hand, in acid solution, the acceptance by the nitrogen atom of a full positive charge suppresses ionization of the tosyl group and formation of intermediates such as CXXXV and CXXXVI. Under these conditions, then, normal displacement of the tosyl group, *with inversion*, occurs.

Similar considerations apply to the conversion of dihydrocinchonine and dihydrocinchonidine to the corresponding *epi* bases under the influence of hot aqueous hydrochloric acid (100, 165) (displacement of $-\text{OH}_2^+$). It may be noted that under these strongly acidic conditions, toxine formation takes place only to a minor extent (*cf.* Section II, 1, *a*).

A large number of 9-chloro and 9-bromo bases has been prepared by the action of phosphorus halides on the various alkaloids (11-14, 56, 97, 134, 135, 151, 166, 167). It seems probable that the replacement of hydroxyl by halogen in these reactions takes place with inversion. The hydrolysis of the halides, which is best carried out with silver nitrate in dilute nitric acid, also appears to involve a change in configuration at C.9 (97). In contrast, treatment of the halides with silver salts in neutral hydroxylic media results in smooth formation of substances of the *hetero* series (*cf.* Section II, 1, *d*).

It might be expected that 9-halo bases differing only in configuration at C.9 would be transformable to geometrically isomeric anhydro compounds (*cf.* Section II, 1, *b*). In fact, possibly for steric reasons, only one product is ordinarily obtained; the isolation of an anhydro base isomeric with dihydrocinchene has been reported, but the product was impure and incompletely characterized (97).

4. DIRECT INTERCONVERSIONS

When quinine is subjected to the action of potassium hydroxide in hot amyl alcohol, a mixture of the four stereoisomeric bases, quinine, *epiquinine*, quinidine and *epiquinidine*, is obtained (168, 169). The same mixture can be obtained in like manner from quinidine. This reaction, which is generally applicable to the cinchona bases, has been shown to take place by an oxidation-reduction mechanism, in which the system quinone-quinidinone is intermediary (156) (*cf.* Section III, 2.). The oxidant necessary for the production of the requisite catalytic amounts of ketones is ordinarily air, but in the absence of the latter, the cinchona base itself may act as an oxidizing agent, presumably through reduction of its pyridine ring. Thus, treatment of quinine with potassium in triethylcarbinol with complete exclusion of air furnishes a reaction product which contains quinidinone, but no detectable amounts of *epiquinine*,

quinidine or *epi*quinidine. This result implies that quinine cannot readily reduce quinidinone. On the other hand, in the presence of metal derivatives of simple primary and secondary alcohols, the isomerization reaction is general, and this fact is consistent with the observation that the ketones are reduced by simple primary and secondary metal alcoholates to mixtures of the hydroxy bases.

Of considerable interest is the observation that in the isomerization of quinine the proportion of quinidine present in the reaction mixture reaches a maximum after a short time, and then diminishes gradually until only a small amount remains. From the behavior of isolated systems, it may be assumed that reduction of the catalytic amounts of ketones present at any time leads mainly to quinine and quinidine, and only a small proportion of *epi* bases. However, since the latter are much more resistant to oxidation by hydride ion transfer processes than their isomers, they continue to accumulate throughout the course of the reaction. The isomerization does not reach a true equilibrium since there are side reactions which lead to the formation of unidentifiable products.

IV. Synthesis

At the time, in the middle of the nineteenth century, when the potentialities of synthetic organic chemistry were becoming apparent, the natural supply of the cinchona alkaloids was variable and undependable. Consequently, great importance was attached to the artificial preparation of the materials. The most famous of the efforts made in that direction, that of W. H. Perkin in 1856, led to the discovery of mauve, and thence to the founding of the organic chemical industry. Perkin's own description of his work provides us with an interesting picture of the state of organic chemical synthesis at that time (170).

At this period much interest was taken in the artificial formation of natural organic substances; but at the time I was at the Royal College of Chemistry, although the theory of compound radicals, the doctrine of substitution, &c. were occupying much attention, very little was known of the internal structure of compounds and the conceptions as to the method by which one compound might be formed from another was necessarily very crude.

Thus, in the Report of the Royal College of Chemistry, published in 1849, Hofmann refers to the artificial formation of quinine as a great desideratum, and then states

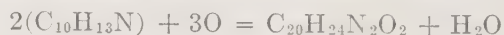
"It is a remarkable fact that naphthalene, the beautiful hydrocarbon of which immense quantities are annually produced in the manufacture of coal gas, when subjected to a series of chemical processes, may be converted into a crystalline alkaloid. This substance, which has received the name of naphthalidine, contains 20 equivalents of carbon, 9 equivalents of hydrogen, and 1 equivalent of nitrogen. (C = 6. O = 8.)

"Now if we take 20 equivalents of carbon, 11 equivalents of hydrogen, 1 equivalent of nitrogen, and 2 equivalents of oxygen, as the composition of quinine, it will be

obvious that naphthalidine, differing only by the elements of two equivalents of water, might pass into the former alkaloid simply by an assumption of water. We cannot, of course, expect to induce the water to enter merely by placing it in contact, but a happy experiment may attain this end by the discovery of an appropriate metamorphic process."

In fact there was but little other ground to work upon in many instances than this kind of speculation.

As a young chemist I was ambitious enough to wish to work on this subject of the artificial formation of natural organic compounds. Probably from reading the above remarks on the importance of forming quinine, I began to think how it might be accomplished, and was led by the then popular additive and subtractive method to the idea that it might be formed from toluidine by first adding to its composition C_3H_4 by substituting allyl for hydrogen, thus forming allyltoluidine, and then removing two hydrogen atoms and adding 2 atoms of oxygen, thus



Allyltoluidine

Quinine

The allyltoluidine having been prepared by the action of allyl iodide on toluidine, was converted into a salt and treated with potassium dichromate; no quinine was formed, but only a dirty reddish-brown precipitate. Unpromising though this result was, I was interested in the action, and thought it desirable to treat a more simple base in the same manner. Aniline was selected, and its sulphate was treated with potassium dichromate; in this instance a black precipitate was obtained, and, on examination, this precipitate was found to contain the coloring matter since so well known as *aniline purple* or *mauve*, and by a number of other names. All these experiments were made during the Easter vacation of 1856 in my rough laboratory at home. Very soon after the discovery of this coloring matter, I found that it had the properties of a dye, and that it resisted the action of light remarkably well.

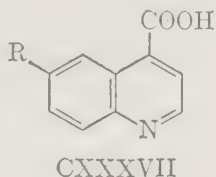
From our present vantage point, it is clear that the problem was one of hopeless complexity for the time. Fifty years were to pass before the structures of the alkaloids were elucidated, and synthetic work could be initiated with reasonable prospects for success.

The synthetic investigations which were undertaken shortly after the turn of the century culminated in the total synthesis of dihydroquinine in 1931, and that of quinine in 1944. During this period the attack proceeded along four main lines. The first great advance was made when it was shown that the cinchona bases could be prepared by partial synthesis from the toxines, which contain two fewer asymmetric centers than the alkaloids themselves. This discovery focussed attention on the development of methods for the synthesis of quinoline 4-ketones from components representing the quinoline and quinuclidine portions of the alkaloid molecules. The synthesis of substances useful in the introduction of the quinoline moiety was accomplished during the early phases of the synthetic studies. The developments along these lines set the stage for the final solutions of the synthetic problem, which were achieved with

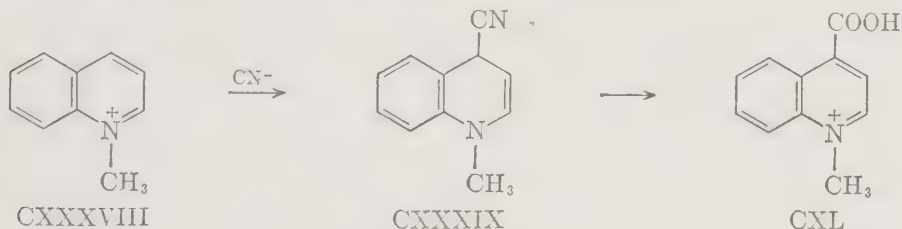
the elaboration of methods for the synthesis of suitable components for the incorporation of the quinuclidine residue.

1. THE QUINOLINE PORTION

The starting point for all syntheses of the cinchona bases and related substances is the quinoline portion of the molecule, represented by cinchoninic acid (CXXXVII, $R = H$) or quininic acid (CXXXVII, $R = OCH_3$). The former product has been obtained from isatin and acetaldoxime (171), by decarboxylation of quinoline-2,4-dicarboxylic

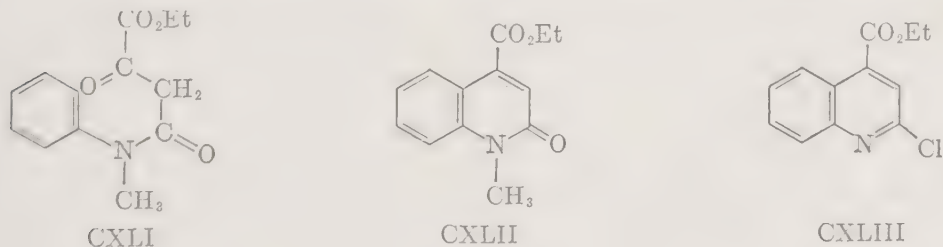


acid (172-174), obtained by condensation of isatinic acid and pyruvic acid, and by oxidation of lepidine (41, 42, 175-177). An interesting synthesis devised by Kaufmann (178-181) proceeded from quinoline, which was converted into the methiodide (CXXXVIII) and thence, by treatment with potassium cyanide, into *N*-methyl-4-cyanoquinoline (CXXXIX) and thence, by oxidation of the latter compound with iodine, followed by hydrolysis, furnished cinchoninic acid methiodide (CXL), which lost



the elements of methyl iodide at 210-220° and was smoothly converted into cinchoninic acid (CXXXVII, $R = H$).

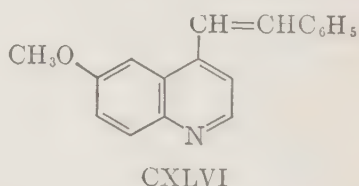
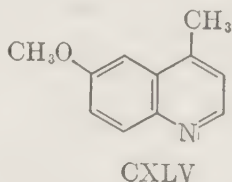
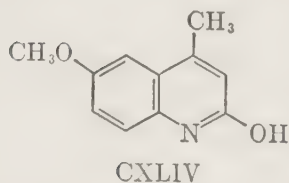
Another synthesis has been described by Thielepape (182), in which *N*-methylacetanilide was condensed with ethyl oxalate to give α -ethoxalyl-*N*-methylacetanilide (CXLI). Cyclization of CXLI with concentrated sulfuric acid furnished 1-methyl-4-carbethoxyquinolone-2 (CXLII),



which on chlorination with phosphorus pentachloride and phosphorus oxychloride yielded ethyl 2-chlorocinchoninate (CXLIII), with simultaneous displacement of the *N*-methyl group. Cinchoninic acid was finally obtained by reductive hydrolysis of CXLIII with stannous chloride and concentrated hydrochloric acid.

The first successful syntheses of quininic acid (CXXXVII, $R = OCH_3$) were achieved independently in 1912 by Kaufmann and Peyer (183), and Pictet and Misner (184). The former group applied to 6-methoxyquinoline the method which they had used earlier in the synthesis of cinchoninic acid from quinoline. Pictet and Misner isolated ethyl quininate in small yield directly from the condensation of *p*-anisidine with formaldehyde and pyruvic acid in the presence of hydrochloric acid.

Numerous other methods for the synthesis of the methoxy acid were developed subsequently. The pyruvic acid-isatin condensation, and the Thielepape synthesis, were extended by the use of appropriately methoxylated starting materials (185, 186). The transformation of *m*-cresol into quininic acid has been reported by Koelsch (187). In 1931 Rabe and co-workers (188, 189) condensed *p*-anisidine with acetoacetic ester and obtained a product, which on cyclization with 90% sulfuric acid gave 2-hydroxy-6-methoxylepidine (CXLIV). Removal of the 2-hydroxyl group was accomplished by successive chlorination and reduction with aluminum and acetic acid. The resulting 6-methoxylepidine (CXLV)

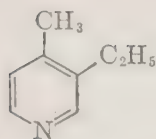


was then converted into 6-methoxy-4-styrylquinoline (CXLVI), which was oxidized to quininic acid with potassium permanganate. The possibilities of this synthesis have subsequently been thoroughly explored (181, 190) and it is probable that the process represents the most satisfactory synthetic route to quininic acid at present available.

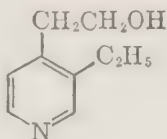
2. THE QUINUCLIDINE PORTION

The synthetic investigations related to the quinuclidine moiety had as their first objectives the synthesis of simple quinuclidine derivatives and degradation products from the alkaloids.

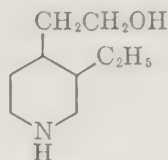
In 1904, Koenigs showed that β -collidine (CXLVII), which was at that time available only from the degradation of cinchonine (47, 58, 59), could be condensed with formaldehyde to give 3-ethyl-4-(β -hydroxyethyl)-pyridine (CXLVIII), which on reduction with sodium and alcohol



CXLVII

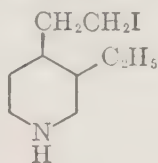


CXLVIII

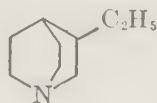


CXLIX

yielded the corresponding hexahydro derivative (CXLIX) (191). The



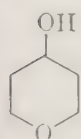
CL



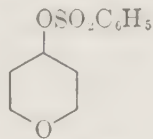
CLI

latter substance was converted by treatment with hydriodic acid and phosphorus into an iodo compound (CL), which was stable only as its salt, and which was transformed into the hydriodide of 2-ethylquinuclidine (CLI) on standing in ether solution. Quinuclidine itself was later synthesized by application of Koenigs' method to γ -picoline (192, 193).

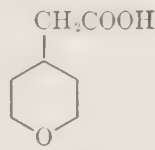
More recently, Prelog (194) has described an ingenious synthesis of quinuclidine, also adapted to the preparation of 2-ethylquinuclidine (195), which employs tetrahydropyranol (CLII) (196) as starting material. The substance was first converted into the corresponding benzene-sulfonyl derivative (CLIII), which was then treated with sodiomalonic ester. Hydrolysis and decarboxylation of the resulting substituted malonate afforded tetrahydropyranyl-4-acetic acid (CLIV). Bouveault



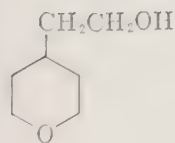
CLII



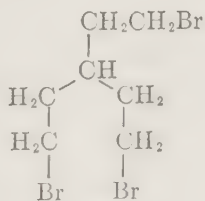
CLIII



CLIV



CLV



CLVI

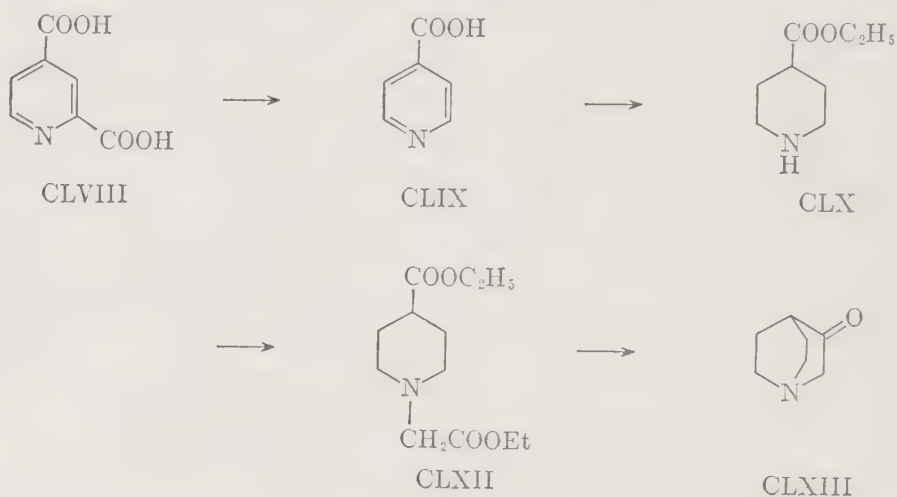


CLVII

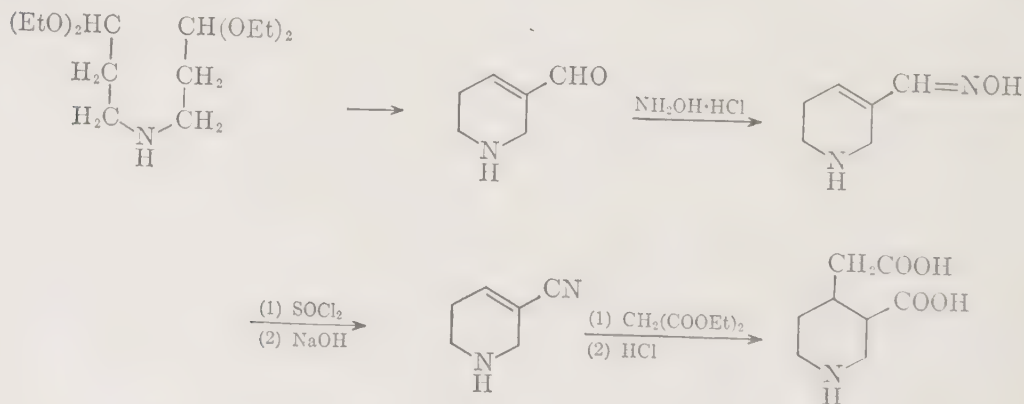
reduction of this material (as the ester) followed by treatment with fuming hydrobromic acid furnished 3-(2-bromoethyl)-1,5-dibromopen-

tane (CLVI), which was converted into quinuclidine (CLVII) by the action of ammonia in methanol. Various modifications of this procedure were also successfully pursued.

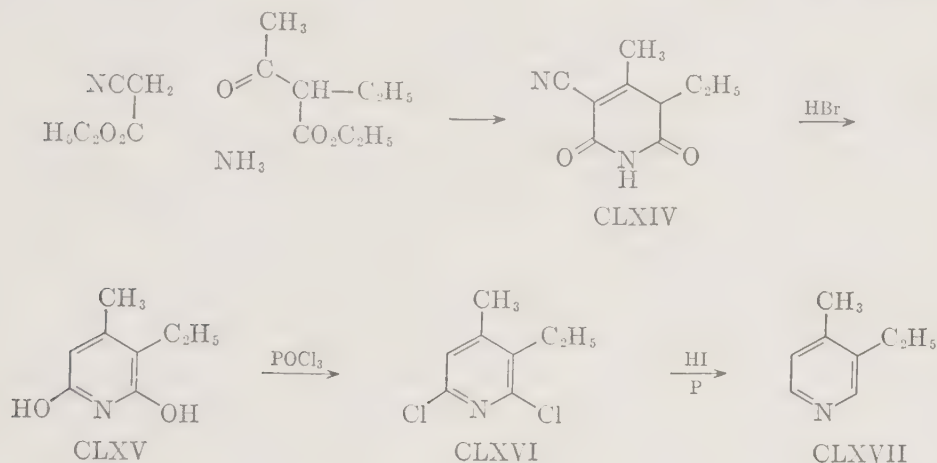
A further synthesis of quinuclidine was devised by Clemo and Metcalfe (197), who decarboxylated 2,4-lutidinic acid (CLVIII), obtained by oxidation of 2,4-lutidine, and reduced the resulting pyridine-4-carboxylic acid (CLIX) with sodium and alcohol. Esterification of the product afforded ethyl piperidine-4-carboxylate (CLX), which was condensed with ethyl chloroacetate to give ethyl piperidine-1-acetate-4-carboxylate (CLXII). Dieckmann cyclization followed by decarboxylation yielded 3-ketoquinuclidine, which on reduction by the Wolff-Kishner or Clemmensen methods gave quinuclidine.



Cincholoiponic acid was the first of the degradation products of the cinchona alkaloids to be synthesized. The synthesis followed the course illustrated in the accompanying chart. The mixture of racemic α - and β -cincholoiponic acids (*cf.* Section III, 1) obtained in this way was separated, and resolved by crystallization of the brucine salts. The *d*- β -cincholoiponic acid proved to be identical with the acid from cinchonine (68, 69).

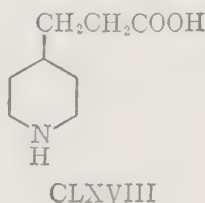


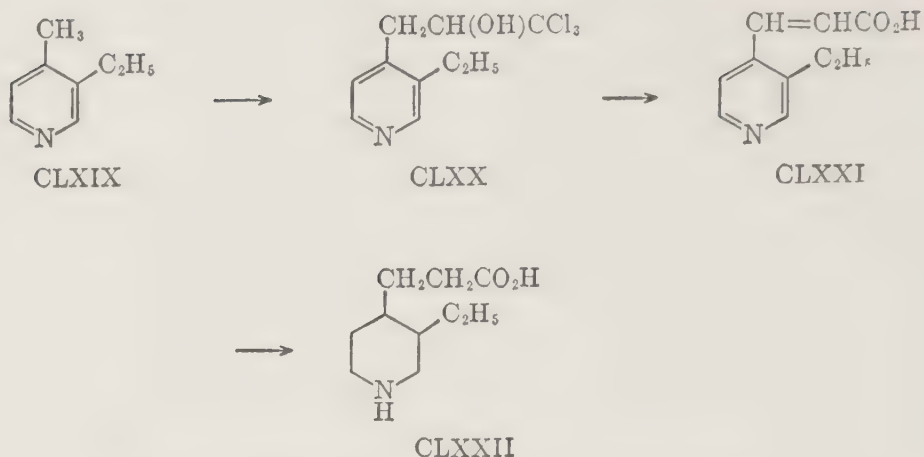
The potentialities of β -collidine as a starting material for the preparation of compounds useful in the synthesis of cinchona alkaloids were recognized at an early date by Koenigs (72, 191). It was, however, not until 1919 that synthesis of this compound was achieved. In that year Ruzicka and Fornasir (198) reported a procedure in which ethyl ethyl-acetoacetate, cyanoacetic ester and ammonia were condensed to give the substituted Guareschi imide (CLXIV), which on hydrolysis and decarboxylation furnished 2,5-dihydroxy-3-ethyl-4-methylpyridine (CLXV). The corresponding dichloride (CLXVI) was prepared from this substance



by the use of phosphorus oxychloride, and β -collidine (CLXVII) was finally obtained by reduction of CLXVI with hydriodic acid and red phosphorus. Numerous other syntheses of this substance have since been recorded (199–203).

An important contribution to the synthetic problem was made in 1921 by E. Koenigs and Ottmann (204), who extended previous work by Rabe and Kindler (205), on the preparation of β -(4-piperidyl)-propionic acid (CLXVIII), to the synthesis of *dl*-homocincholoipon (CLXXII). β -Collidine (CLXIX) was condensed with chloral, and an intermediate (CLXX) was obtained which yielded β -(3-ethylpyridyl)-4-acrylic acid (CLXXI) on alkaline hydrolysis. Reduction of this product with sodium and amyl alcohol furnished a mixture from which *dl*-homocincholoipon (CLXXII) could be isolated.

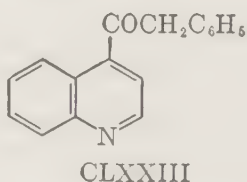




3. 4-QUINOLYLKETONES AND THE TOXINES

We consider now the methods which were developed for the combination of components representing the quinoline and quinuclidine portions of the alkaloid molecules.

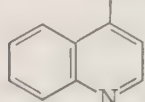
In 1912, Rabe described the reaction of ethyl cinchoninate with benzylmagnesium chloride, from which benzyl-(4-quinolyl)-ketone (CLXXIII) was obtained in small amounts (206), accompanied by the



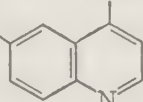
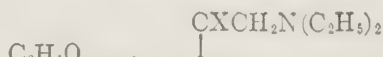
tertiary alcohol resulting from further attack by the Grignard reagent. This is apparently the first example of successful synthesis of a ketone from an ester by the Grignard procedure, although a product (m.p. 294°) described as phenyl-(4-quinolyl)-ketone had been obtained earlier by Remfry and Decker (207) from ethyl cinchoninate and phenylmagnesium bromide. Subsequent investigation of this reaction by Rabe and Pasternack (208) revealed that phenyl-(4-quinolyl)-ketone is indeed formed, but that the melting point of this compound is 60° .

In connection with their work on the synthesis of quinic acid and of cinchoninic acid, Kaufmann and his collaborators (178-180, 184) had prepared 4-cyano-6-methoxyquinoline and 4-cyanoquinoline, obtained earlier by dehydration of cinchoninamide with thionyl chloride or with phosphorus pentoxide (209). Both products reacted with methylmagnesium iodide in anisole solution and furnished methyl-(6-methoxy-4-quinolyl)-ketone and methyl-(4-quinolyl)-ketone respectively (210, 211). Like Rabe (206), these investigators were cognizant of the synthetic

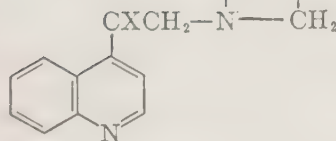
possibilities of such derivatives, and were further impressed by the presence of the alkylaminoethanol function as a common structural feature in the cinchona bases and in other physiologically active compounds, for example, adrenalin. Accordingly, they undertook the preparation of various aminoketones and aminoalcohols represented by formulae CLXXIV-CLXXVI ($X = O$ or H, OH) (212, 213). With the exception of CLXXIV, which was obtained by reduction of the isonitrosoketone, all the products were derived from the bromoketone (CLXXVII) by alkylation of the appropriate amine. Similar experiments were simultaneously carried on by Rabe (208, 214), who condensed bromomethyl-(4-quinolyl)-ketone (CLXXVII, $R = H$) with cincholoiponic acid ethyl



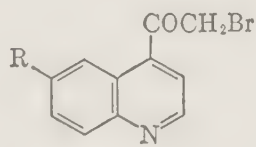
CLXXIV



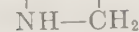
CLXXV



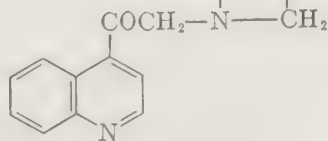
CLXXVI



CLXXVII



CLXXVIII

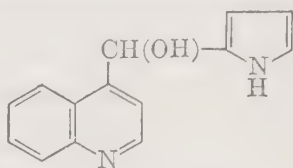


CLXXIX

ester (CLXXVIII) and obtained an aminoketone (CLXXIX) which was reduced to the corresponding aminoalcohol in the presence of palladium black.

The extensive further literature on the preparation of analogues possessing the ethanolamine structure characteristic of the cinchona

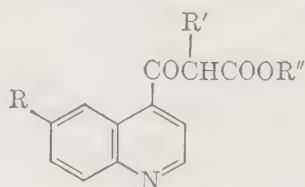
bases is mentioned here only briefly. In 1917 Karrer (215) carried out the reaction of cinchoninyl chloride hydrochloride with pyrrolmagnesium iodide and obtained 4-quinolyl-(2-pyrrolyl)-ketone, which on reduction with zinc dust and acid furnished the quinolylpyrrolecarbinol (CLXXX). Numerous α -(alkylaminomethyl)-4-quinolinemethanols were synthesized during World War II in connection with a search for effective antimalarial



CLXXX

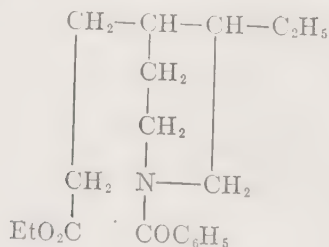
agents. In the preparation of these substances haloketones derived from quinoline-4-carboxylic acids by the diazomethane synthesis were generally used. The haloketones were then reduced to the corresponding halohydrins by the Meerwein-Ponndorf procedure, and condensed with the appropriate amines (216).

A very significant synthetic advance was made when Rabe and Pasternack showed in 1913 that aliphatic esters could be condensed smoothly with ethyl cinchoninate, to give β -keto esters (CLXXXI) from

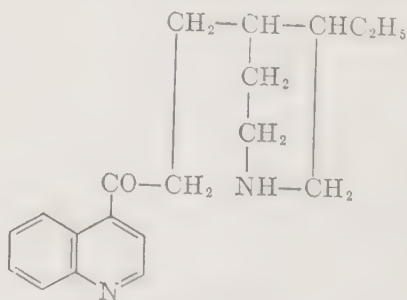


CLXXXI

which quinoline-4-ketones were readily preparable by hydrolysis and decarboxylation (217). In 1918 Rabe and Kindler (218) condensed the quinoline ester with *N*-benzoylhomocincholoipon ethyl ester (CLXXXII), which had been obtained earlier by permanganate oxidation of *N*-benzoyldihydrocinchotoxine methylsulfomethylate (*cf.* Section II, 1, *a*). Decarboxylation of the condensation product furnished dihydrocinchotoxine



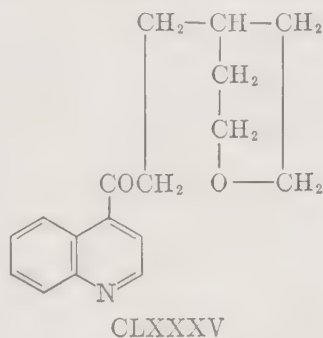
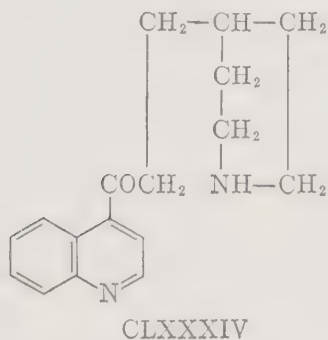
CLXXXII



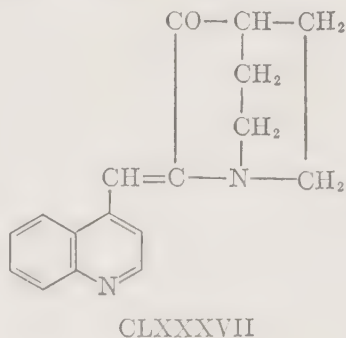
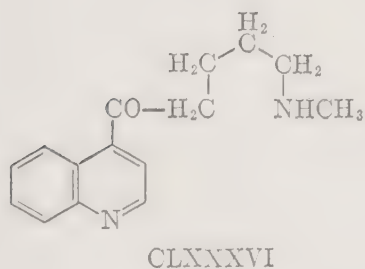
CLXXXIII

(CLXXXIII). The same series of reactions was subsequently applied to ethyl quininate (205), which furnished dihydroquinotoxine. Some twenty-five years later partial synthesis of quinotoxine itself was achieved in like manner by Proštenik and Prelog (90), who condensed ethyl quininate with *N*-benzoylhomomeroquinene ethyl ester, derived by Beckmann rearrangement from *N*-benzoylcinchotoxine oxime.

A number of related condensations deserve mention. From β -(piperidyl-4-) propionic acid (205), the vinyl-free ketobase rubatoxine (CLXXXIV) was prepared (219). Ethyl cinchoninate has been condensed with



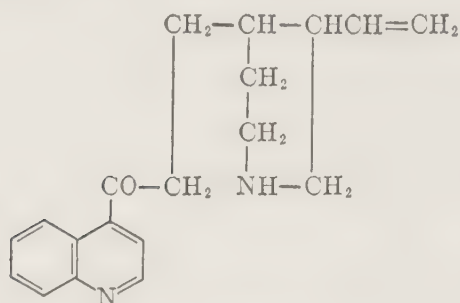
ethyl β -(tetrahydropyranyl-4)-propionate, to obtain CLXXXV (220), while *N*-methylpiperidone has been employed in the synthesis of CLXXXVI by a similar method (221, 222). A related condensation is that of Clemo and Hoggarth, who condensed 3-ketoquinuclidine (*cf.* Section IV, 2) with quinoline-4-aldehyde, and obtained CLXXXVII (223).



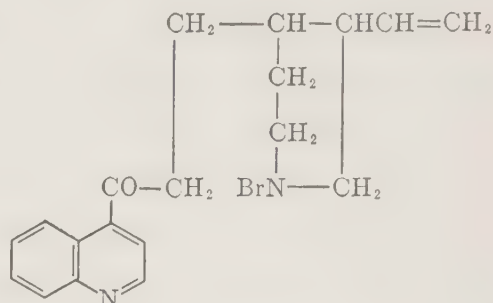
4. CONVERSION OF THE TOXINES TO THE ALKALOIDS

Rabe in 1911 succeeded in converting cinchotoxine (CLXXXVIII) into cinchonidinone (CXC) (224), (which had earlier been reduced to cinchonine (76)), by treatment of the toxine with hypobromous acid, followed by cyclodehydrobromination of the resulting *N*-bromo derivative (CLXXXIX) with sodium ethoxide. The same sequence of reactions served for the conversion of dihydrocinchotoxine into dihydrocin-

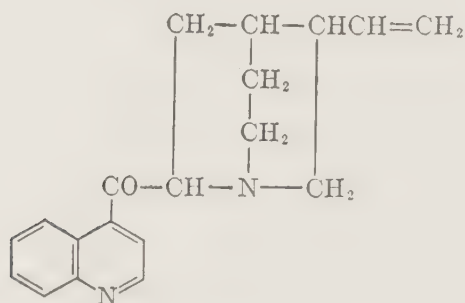
chonine (225). Seven years later the reconversion of quinotoxine into quinidinone was similarly accomplished (226), and reduction of the latter compound with aluminum powder and ethyl alcohol in the presence of sodium ethoxide afforded a mixture of stereoisomeric alcohols, from which quinine and quinidine were isolated.



CLXXXVIII

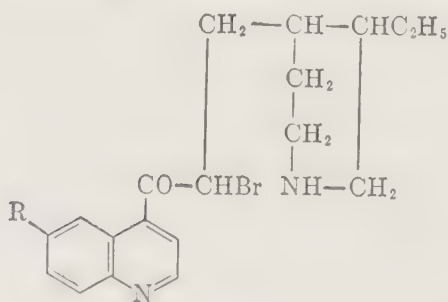


CLXXXIX

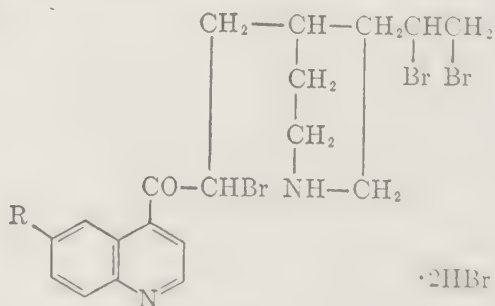


CXC

Parallel experiments were carried out by Kaufmann and his associates (227, 228), who brominated dihydrocinchotoxine in 48% hydrobromic acid. The products obtained in this way were *C*-bromo derivatives (CXCI), which on treatment with sodium alkoxide were smoothly converted into dihydrocinchonidinone, and into dihydroquinidinone, respectively. This procedure was applicable only to those compounds



CXCI



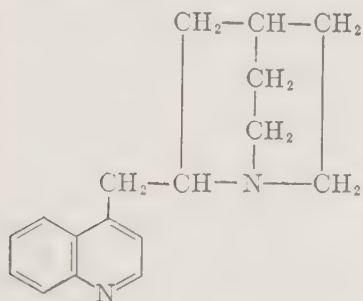
CXCH

·2HBr

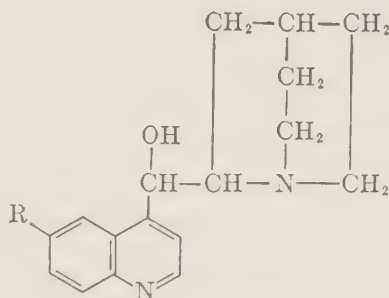
not containing a vinyl group at C.3 until Ludwiczakówna (229) showed that both cinchotoxine and quinotoxine on bromination under these conditions give crystalline tribromo dihydrobromides (CXCII). Treatment of these derivatives with sodium ethoxide for thirty minutes effected cyclization to 10,11-dibromocinchon(id)inone and to 10,11-dibromoquin(id)inone, which were debrominated by the action of sodium iodide, and gave cinchonidinone and quinidinone.

The reduction of cinchona ketones to the alkaloids has recently been shown to proceed very smoothly with sodium *isopropoxide* in toluene (94).

Similar methods have been used in syntheses (219, 230-232) from rubatoxine and its 6'-methoxy derivative (*cf.* Section IV, 3) of a large number of derivatives of ruban (CXCIII) [named (146) from the plant family Rubiaceae, in members of which the cinchona alkaloids occur]. Thus, all four of the optically active 9-rubanols (CXCIV, R = H), as well as the corresponding 6'-methoxy derivatives (CXCIV, R = OCH₃) have been prepared.



CXCIII



CXCIV

5. TOTAL SYNTHESIS OF DIHYDROQUININE

The outstanding contributions of Rabe to the study of the cinchona alkaloids were crowned by the achievement in 1931 of the total synthesis of dihydroquinine (188). The methods used had been developed over the course of a quarter of a century. During this time, as has been indicated in previous sections, processes had been discovered for the synthesis of quinic acid and *dl*-homocincholoipon. Reactions had been found which served for the condensation of such components, and for the transformation of the resulting toxins into natural alkaloids.

The key stage of the final effort was the preparation of *dl*-homocincholoipon in sufficient quantity for resolution, which was carried out through the *d*-tartrates of the corresponding ethyl ester. The resulting (+)-homocincholoipon ester was converted into dihydroquinotoxine, and thence, by way of the *C*'-bromo derivative, into dihydroquinidinone.

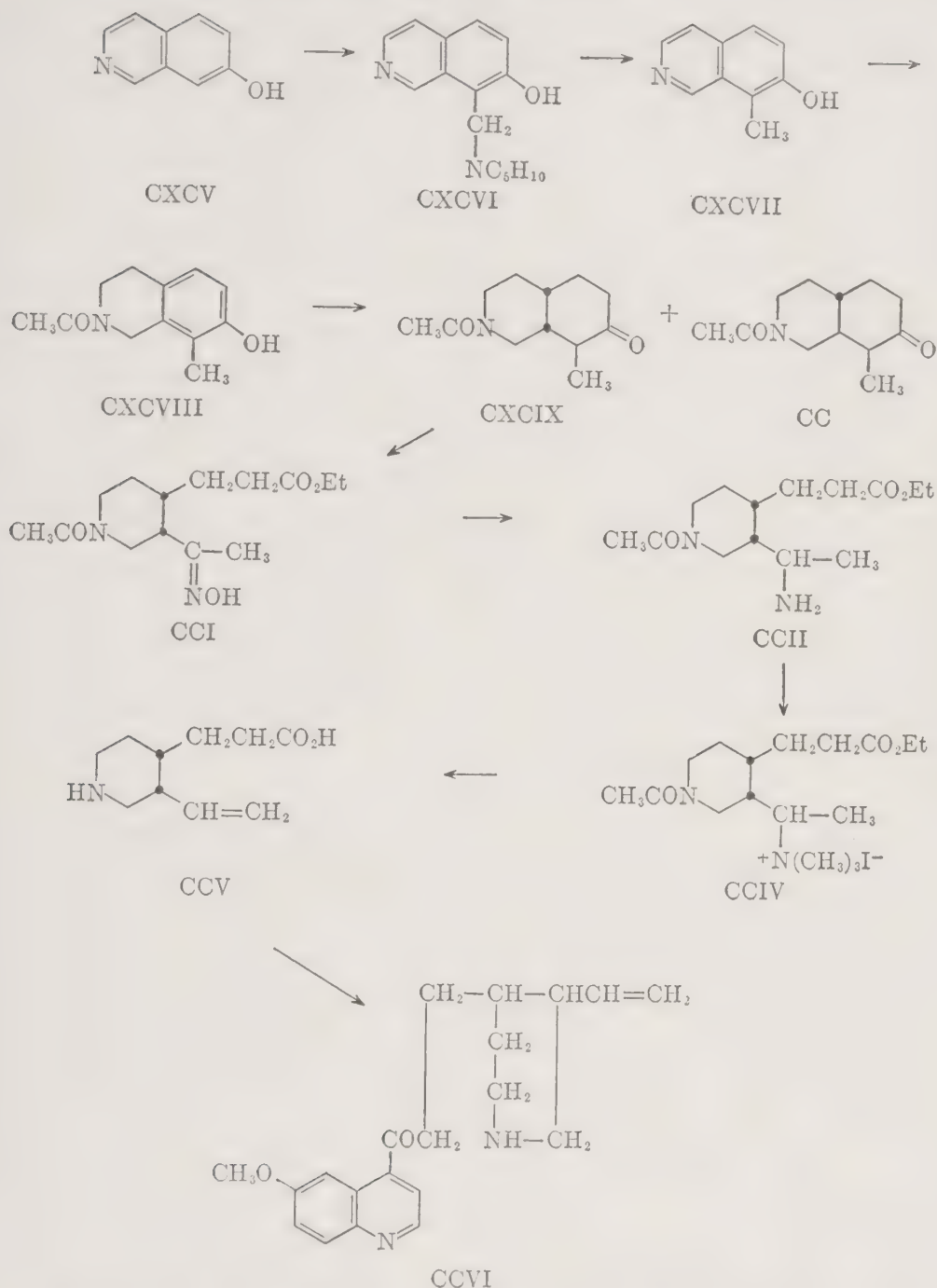
Catalytic hydrogenation of the carbonyl group in the presence of palladium gave dihydroquinine, identical in all respects with the naturally occurring alkaloid. In addition, dihydroquinidine and a stereoisomer, subsequently identified as *epidi*hydroquinidine (154, 155), were also isolated. Further examination of the reduction mixture revealed the presence of *epidi*hydroquinine, and it was shown that the four isomers are likewise formed in the reduction of dihydroquinidinone with a mixture of aluminum, sodium ethoxide and alcohol.

6. TOTAL SYNTHESIS OF QUININE

Through the investigations described in the preceding sections, the problem of the total synthesis of quinine had been reduced to that of the synthesis of homomeroquinene. This goal was reached in 1944 (233).

The starting point for the synthetic work was 7-hydroxyisoquinoline (CXCXV) which was obtained by condensation of *m*-hydroxybenzaldehyde and aminoacetal, followed by cyclization with sulfuric acid. The carbon atom required for completion of the homomeroquinene skeleton was introduced by condensation of CXCXV with formaldehyde and piperidine. 7-Hydroxy-8-piperidinomethylisoquinoline (CXCXVI) was obtained in this way, and was smoothly converted into 7-hydroxy-8-methylisoquinoline (CXCXVII) by treatment with methanolic sodium methoxide at 220°. On catalytic hydrogenation in acetic acid solution CXCXVII absorbed two moles of hydrogen and, after acetylation with acetic anhydride in methanol, furnished an *N*-acetyltetrahydro derivative (CXCXVIII). High pressure reduction of CXCXVIII over Raney nickel afforded a mixture of stereoisomeric *N*-acetyl-7-hydroxy-8-methyldecahydroisoquinolines. Direct oxidation of the crude hydrogenation product yielded a mixture of ketones (CXCXIX) and (CC), from which the *cis* form (CXCXIX) was separable as a crystalline hydrate. Rupture of the carbocyclic ring was brought about by sodium ethoxide and ethyl nitrite, and furnished *N*-acetyl-10-oximinodihydrohomomeroquinene ethyl ester (CCI). The oximino-ester was then hydrogenated to the corresponding amino-ester (CCII).

N-Acetyl-10-aminodihydrohomomeroquinene ethyl ester (CCII) was converted into *N*-acetyl-10-trimethylammoniumdihydrohomomeroquinene ethyl ester iodide (CCIV) by treatment with methyl iodide and potassium carbonate. With 60% potassium hydroxide elimination occurred according to the Hofmann rule and, after treatment with potassium cyanate, homomeroquinene (CCV) was isolated from the reaction mixture as the *N*-uramido derivative. Regeneration of the homomeroquinene was accomplished by hydrolysis with dilute acid, and in this way, *cis*-*dl*-homomeroquinene was obtained.



Resolution into optically active forms was not attempted at this point, but the product was converted into *dl*-*N*-benzoylhomomeroquinene ethyl ester and condensed with ethyl quininate in the presence of sodium ethoxide. The *dl*-quinotoxine obtained on hydrolysis of the condensation product was resolved by crystallization of the dibenzoyl-*d*-tartrates,

and furnished *d*-quinotoxine identical in all respects with the natural material. This synthesis, together with the previously established conversion of *d*-quinotoxine into quinine, completed the total synthesis of the latter alkaloid.

V. Minor Alkaloids

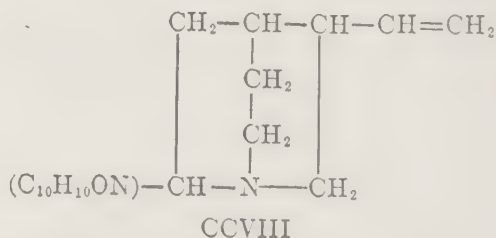
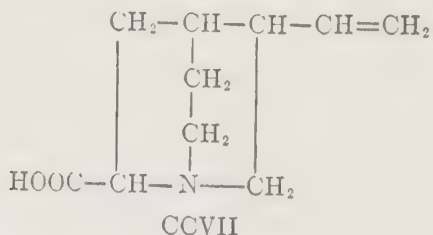
Epiquinine, *epiquinidine*, *heteroquinine* and *quinotoxine* have been isolated from cinchona preparations in very small quantities (101, 234, 235), but it is not certain that these materials are not artifacts. The dihydrobases corresponding to the major alkaloids, on the other hand, always accompany the vinyl bases (29, 236, 237), from which they are best separated by treatment with mercuric acetate (90, 238, 239). The phenolic base *cupreine* (= *demethylquinine*) is also a natural product (240–242).

Each of the above substances is closely related to the major alkaloids. A number of additional bases (243) has been isolated whose relation to cinchonine or quinine is more remote, or obscure. Except in the cases of *cinchonamine*, *quinamine*, and *conquinamine* little is known of most of these alkaloids beyond their empirical formulae, and the status of some of them as chemical individuals may be open to question.

1. CINCHONAMINE

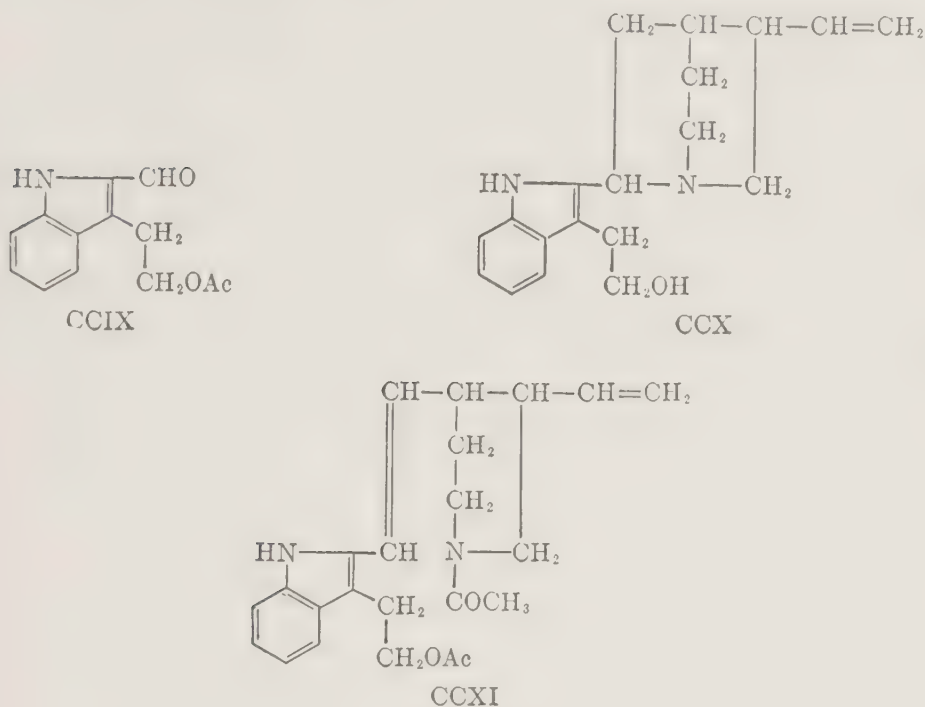
Arnaud first isolated cinchonamine, in 1881, and showed that it possesses the formula $C_{19}H_{24}ON_2$ (244–247). Its structure was determined by Goutarel, Janot, Prelog, and Taylor in 1950 (248).

Cinchonamine gives color reactions typical of the indole alkaloids (249), and differs from all of the major cinchona bases in that it is oxidized by chromic acid to an acid, (CCVII), containing an intact quinclidine residue, which was first obtained by the oxidation of quinamine (*cf.* Section V, 2). This result implies structure CCVIII for the alkaloid.

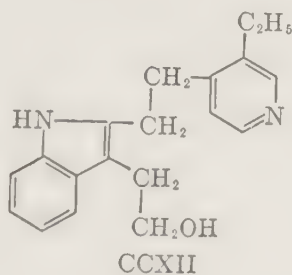


The nature of the residue $C_{10}H_{10}ON$ was shown by conversion of cinchonamine through vigorous treatment with acetic anhydride to diacetyl-

allocinchonamine, from which by oxidation 2-(β -acetoxyethyl)-indole-1-aldehyde (CCIX) was obtained. Cinchonamine is thus CCX, and diacetyl*allocinchonamine* CCXI.



When cinchonamine is heated with selenium or palladium-charcoal, it loses two hydrogen atoms, and is converted smoothly to dehydrocinchonamine (CCXII); the change is reminiscent of the transformation of quinuclidine itself to γ -ethylpyridine (250).

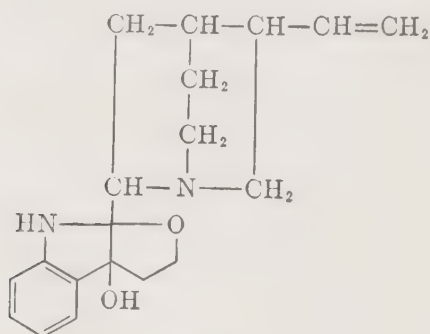


2. QUINAMINE AND CONQUINAMINE

The isomeric bases, quinamine and conquinamine, of the formula $C_{19}H_{24}O_2N_2$, were isolated in 1872 and 1877 by Hesse (251).

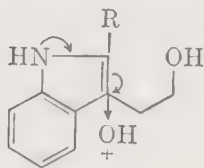


Kirby showed that quinamine and the substances derived from it gave indole color reactions, and isolated 2,3-dimethylindole from zinc dust distillation of the alkaloid (252). Henry, Kirby, and Shaw oxidized quinamine with chromic acid, and obtained the quinuclidine acid (CCVII) (253). It was thus clear that quinamine contained the vinylquinuclidine system of the major cinchona alkaloids, attached to an easily oxidizable residue, $C_{10}H_{10}O_2N$ (*cf.* Section V, 1). Decisive clarification of the character of the residue was achieved, and quinamine was shown to have the structure CCXIII, when Goutarel, Janot, Prelog, and Taylor found (248) that quinamine is reduced to cinchonamine (CCX) by lithium

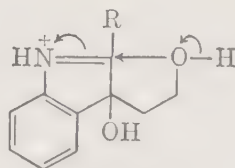


CCXIII

aluminum hydride, and Witkop showed that the reverse change can be brought about by peracetic acid (254). The latter reaction may be presumed to involve an attack (CCXIV) on the β -position of the indole ring of cinchonamine by OH^+ , or an equivalent, with the formation of an intermediate, whose charge may be dissipated through attack at C.2 by the spacially apposite hydroxyl group (CCXV). The reduction of the more highly oxygenated alkaloid to cinchonamine becomes readily



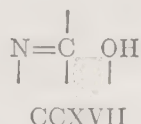
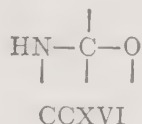
CCXIV



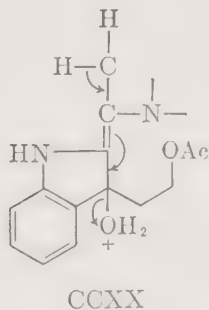
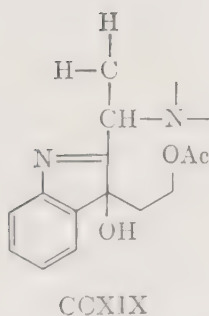
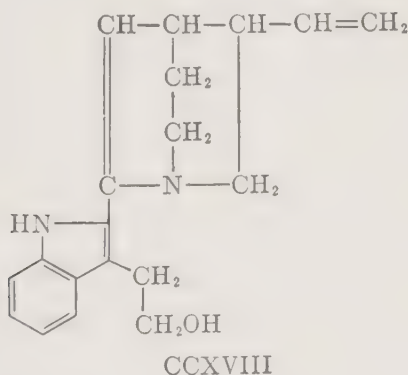
CCXV

explicable when it is considered that the grouping CCXVI may be reduced directly, or as the ring-chain tautomeric system (CCXVII), and

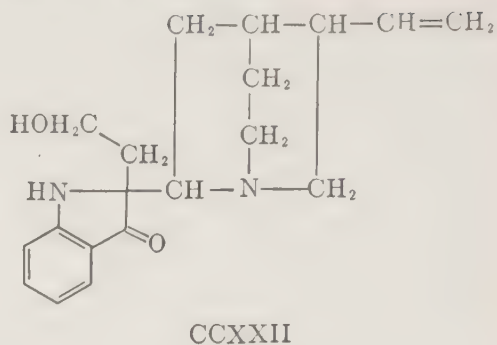
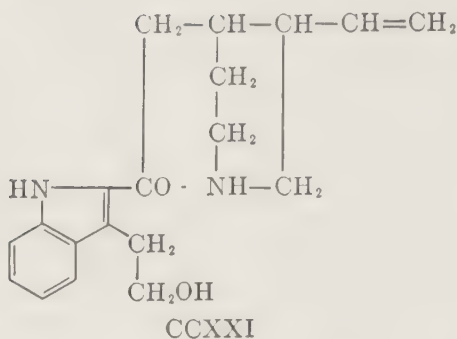
that the resulting β -hydroxydihydroindole will suffer ready loss of water, with aromatization to an indole derivative.



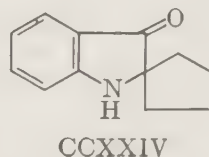
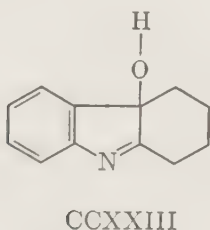
The structure CCXIII provides a satisfactory basis for the interpretation of other transformations of quinamine. When the alkaloid is treated with acetic anhydride or acetyl chloride, acetyl*apo*quinamine is formed (253). From the acetyl derivative, the doubly unsaturated base *apo*quinamine, $\text{C}_{19}\text{H}_{22}\text{ON}_2$, can be obtained. The *apo* base may be formulated as CCXVIII, and the changes (CCXIII \rightarrow CCXIX \rightarrow CCXX) may be envisaged for the formation of its acetyl derivative from quinamine.



The ketobase quinamicine, $\text{C}_{19}\text{H}_{24}\text{O}_2\text{N}_2$, which is obtained when either quinamine or *apo*quinamine is heated with dilute acetic acid, is satisfactorily represented by structure CCXXI. The transformation of quinamine to isoquinamine (255), for which the structure CCXXII has been



considered, may involve a change analogous to that of 11-hydroxy-tetrahydrocarbazolenine (CCXXIII) into 2,2-tetramethyleneisoindoxyl (CCXXIV) (256).

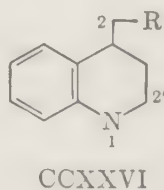
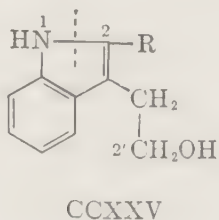


Conquinamine is convertible to *apo*quinamine (CCXVIII) and quinamicine (CCXXI). It is therefore a stereoisomer of quinamine (CCXIII), and differs in configuration from the latter at one or more of the asymmetric centers present.

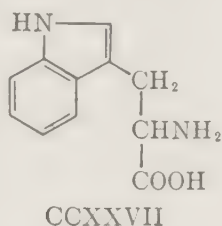
VI. Biogenetic Relationships

Goutarel, Janot, Prelog, and Taylor have suggested that the structure of cinchonamine provides an important clue to the nature of the processes by which the cinchona alkaloids are produced in the plant (248).

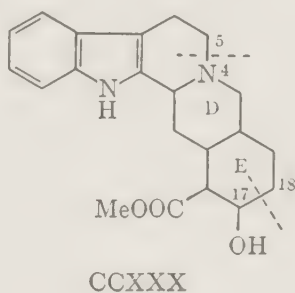
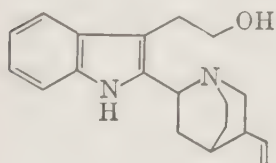
It will be noted that in a formal sense, cinchonamine (CCXXV \equiv CCX) may be converted to a substance having the normal cinchona skeleton (CCXXVI) through cleavage of the N.1-C.2 bond, followed by formation of a new link between N.1 and C.2', after rotation of the benzenoid ring. This relationship indicates that cinchonamine repre-



sents a relatively early stage, or an offshoot, in the biogenesis of the cinchona alkaloids, and provides strong support for the view that the quino-line rings of the major bases are derived from tryptophane (CCXXVII).

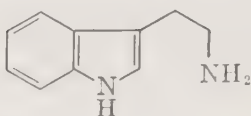
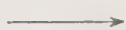


The origin of the quinuclidine moiety of the cinchona alkaloids is suggested by the close structural relationship between the skeleton of cinchonamine (CCX \equiv CCXXIX) and that present in yohimbine

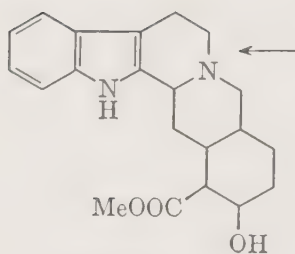
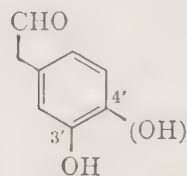
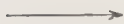


(CCXXX). Thus, in a formal sense, cleavage of CCXXX at C.17-C.18 and C.5-N.4, and formation of a new bond between N.4 and C.17, leads to the skeleton of the cinchona base. Since rings D and E of yohimbine are very probably derived, as indicated in the accompanying chart, from (di)hydroxyphenylalanine and glycine (257-259), or from natural progenitors or congeners of these amino acids, it is likely that the vinyl-quinuclidine system of the cinchona alkaloids derives from the same sources. The cooperation of tryptophane, dihydroxyphenylalanine, and glycine is also involved in the biosynthesis of the alkaloids of the strychnos group (260), and it is noteworthy that a special feature of this latter case, namely, the cleavage of the C.3-C.4 bond of the dihydroxyphenyl ring, is entirely analogous to the change required for the conversion of the yohimbine D, E ring system to the quinuclidine array of the cinchona group. It may be noted further that a similar cleavage is undoubtedly a factor in the formation of the ipecacuanha alkaloids, for example, emetine

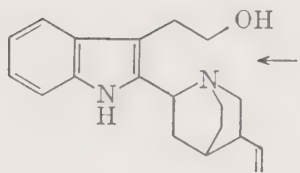
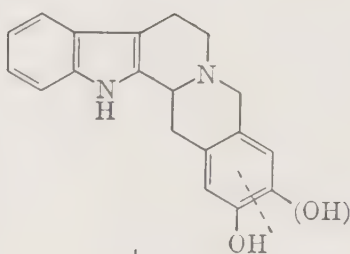
Tryptophane

 CH_2O
 \longleftarrow Glycine

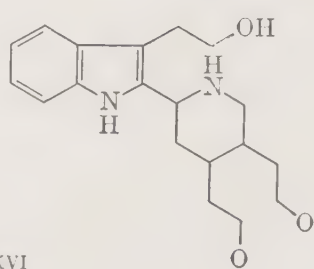
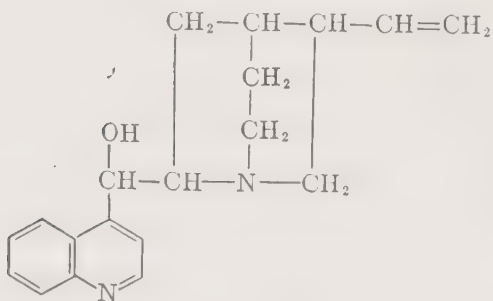
(Di)hydroxyphenylalanine



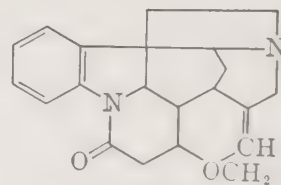
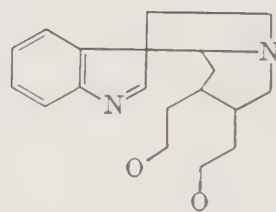
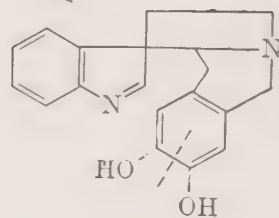
Yohimbine



Cinchonamine

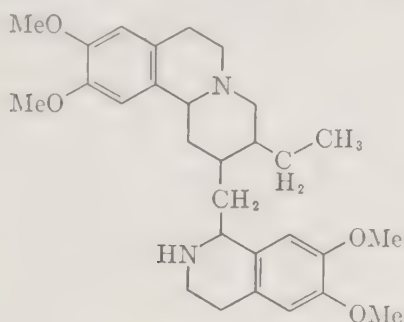

 \downarrow cf. CCXXV \rightarrow CCXXVI


Cinchonine

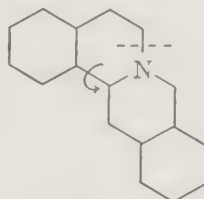


Strychnine

(CCXXXI), from precursors which lead also to simpler alkaloids having the berberine skeleton (CCXXXII) (261).

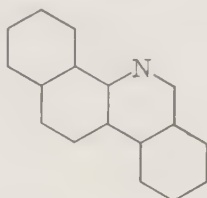


CCXXXI



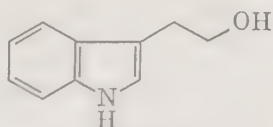
CCXXXII

Finally, analogy for the cleavage of ring C of the yohimbine skeleton at C.5-N.4 may be found in processes which relate the berberine (CCXXXII) and the benzophenanthridine (CCXXXIII) groups.

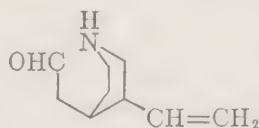


CCXXXIII

A great many variants of the general schemes outlined here may of course be considered. Thus, in cinchona biogenesis we may envisage the prior cooperation of dihydroxyphenylalanine and glycine in the formation of a bicyclic intermediate convertible by cleavage of the carbocyclic ring to 3-vinylpiperidyl-4-acetaldehyde (CCXXXV), or an equivalent. It has been suggested that condensation of the aldehyde group of the latter with quinoline-4-methanol (262), or of the active methylene group and the imino group with the aldehyde function of tryptophal (263), may be involved in the biosynthesis of the cinchona bases. In the light of recent developments, these suggestions may be modified by substitution of tryptophol (CCXXXIV) as the second component. But in the present



CCXXXIV



CCXXXV

state of our knowledge of biogenesis, the specification of the exact nature of the intermediates, or the order in which they enter the biogenetic

scheme, is not possible. None the less, the striking conclusion seems justified that three great classes of alkaloids, the cinchona, yohimbé, and strychnos groups, are formed from common precursors by variants of the same fundamental processes.

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CHAPTER 17

Quinoline Alkaloids, other than those of Cinchona

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	<i>Page</i>
I. Introduction	66
II. Echinopsine	66
1. Occurrence and Isolation	66
2. Physical, Chemical, and Physiological Properties.	66
3. Determination of Structure	67
a. Degradation.	67
b. Synthesis.	68
III. The Furoquinoline Group	69
1. Occurrence and Isolation	69
a. Dictamnine.	69
b. Skimmianine	69
c. γ -Fagarine	69
d. Acronycidine	70
2. Physical, Chemical, and Physiological Properties.	70
a. Dictamnine.	71
b. Skimmianine	71
c. γ -Fagarine	71
3. Determination of Structure	72
a. Behavior towards Alkyl and Acyl Halides.	72
b. Oxidation.	73
4. Attempted Synthesis of Dictamnine: ψ -Dictamnine.	75
5. Table of Physical Constants.	76
6. Addendum	78
IV. Alkaloids of Angostura Bark	80
1. Occurrence and Isolation	80
2. Physical and Chemical Properties; Color and Precipitation Reactions	82
a. Cusparine.	82
b. Galipine	83
c. Cuspareine	83
d. Galipoidine.	84
e. Minor Bases	84
3. Determination of Structure	84
a. Degradation of Cusparine.	84
b. Degradation of Galipine	85
c. Synthesis of Cusparine and Galipine	87
d. Galipoline.	88
e. 4-Methoxy-2- <i>n</i> -amylquinoline and 2- <i>n</i> -Amylquinoline	89
f. Cuspareine and Galipoidine.	90
4. Biogenesis of the Angostura Alkaloids.	92
5. Table of Physical Constants.	94
V. References.	98

I. Introduction

With one exception, the alkaloids discussed in this chapter are all derived from members of the Rutaceae, and they can be classified chemically into two groups. The members of one group are methoxylated derivatives of (2,3-*b*)-furoquinoline, the most widely distributed being the trimethoxy compound, skimmianine. Several recently discovered members of this group are described in an Addendum (p. 78); two of these are furopyranoquinolines closely related structurally to the other alkaloids of the group. A structural relationship is also apparent between these alkaloids and the acridone alkaloids which often occur with them. The second group comprises the numerous alkaloids of *Angostura* bark; apart from some simpler quinoline bases, these are 2-substituted 4-methoxyquinolines.

All the principal alkaloids of both groups possess as a common structural feature the 4-methoxyquinoline unit, in consequence of which they undergo a typical isomerization to *N*-methyl-4-quinolones on vigorous treatment with methyl iodide. This reaction, which has been of considerable assistance in the elucidation of the structures of the alkaloids, also provides a chemical relationship with the alkaloid of *Echinops* species (*Compositae*), which was shown to be *N*-methyl-4-quinolone itself. The isomeric *N*-methyl-2-quinolone occurs in *Angostura* bark.

II. Echinopsine

1. OCCURRENCE AND ISOLATION

The alkaloid echinopsine was isolated in 1900 by M. Greshoff (1) from the seeds of the blue globe thistle, *Echinops ritro* L. (*Compositae*), and its presence was also demonstrated in 14 other species of *Echinops*.

The seeds, freed from husks and powdered, are extracted first with petrol to remove a fatty oil (about 27.5%), then with cold or hot 95% alcohol containing 3% of acetic acid. The residue left on evaporation of the alcohol is dissolved in water, and the filtered solution is made alkaline and extracted with chloroform. Evaporation of the chloroform extract yields yellowish crystals (about 0.5%) which are purified by crystallization from water (charcoal) or benzene.

Small quantities of three other bases, β -echinopsine (m.p. 135°) echinopseine and echinops-fluorescine were also isolated. These substances have not been further investigated.

2. PHYSICAL, CHEMICAL, AND PHYSIOLOGICAL PROPERTIES

Echinopsine forms faintly yellow crystals which separate from water as a monohydrate. It is soluble in 60 parts of water at 15°, and in 6 parts

at 100°. It is readily soluble in the lower alcohols and in chloroform, but very sparingly so in ether (1:600). It dissolves in 10 parts of hot benzene, but is almost insoluble in the cold solvent. The alkaloid is optically inactive.

Echinopsine is a weak base. Solutions of its salts, which exhibit no fluorescence, give precipitates with the usual alkaloid reagents, although not at great dilution. The most sensitive reagents are iodine and phosphomolybdic acid; the former has been employed for investigating the distribution of the alkaloid in the tissues of *Echinops* (1). With ferric chloride, the alkaloid gives an intense blood-red coloration. G. Klein and F. Schusta (2) have described methods for the microchemical detection of the alkaloid.

Various salts are described in Table 1; in addition, M. Greshoff (1) prepared the sulfate, which separates from water either as a dihydrate or as an octahydrate, both forming long needles, the nitrate (trihydrate), and the neutral oxalate (tetrahydrate). The salts have a bitter taste and are poisonous. In its toxic action the alkaloid resembles a mixture of strychnine and brucine.

TABLE 1
THE PHYSICAL CONSTANTS OF ECHINOPSINE AND ITS DERIVATIVES

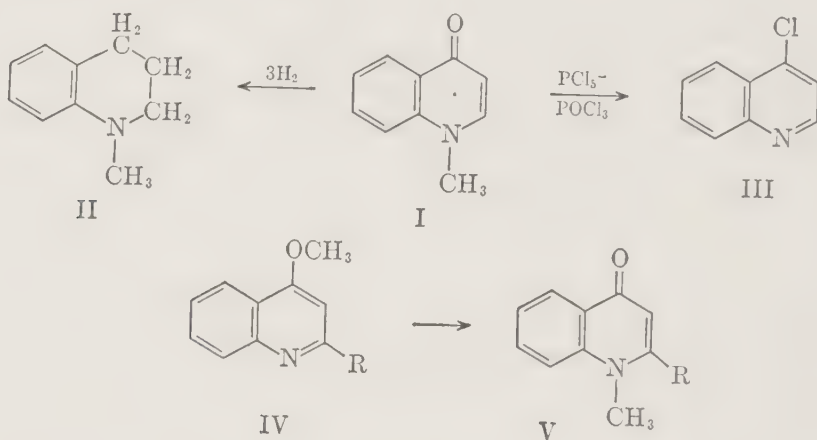
Compound	M.p., °C.	Crystal Form	References
Echinopsine			
(Anhydrous)	152	Feathery needles (C ₆ H ₆)	1, 3
(Monohydrate)	About 90	Clear rhombic crystals (H ₂ O)	1, 5
Aurichloride	168–170	Light yellow needles (dil. HCl)	5
Chloroplatinate	210–212	Orange-yellow needles (dil. HCl)	3, 5
Hydrochloride			
(Anhydrous)	185–186	Crystals (acetone-methanol)	3
(Dihydrate)		Large rhombs (H ₂ O)	1
Mercurichloride	204	Crystalline (dil. HCl)	1, 5
Mercuri-iodide	178	Yellowish (C ₂ H ₅ OH-H ₂ O)	1
Periodide	About 135	Coffee-colored powder (C ₂ H ₅ OH)	1
Picrate	223–224	Yellow crystals (C ₂ H ₅ OH)	3, 1

3. DETERMINATION OF STRUCTURE

a. Degradation. M. Greshoff (1) assigned to the alkaloid the molecular formula C₁₁H₉ON, and suggested, on the basis of its chemical and pharmacological similarity to known lactams such as piperidone, that it might possess the structure of a phenylpyridone. Attempts to confirm such a structure by oxidation and zinc dust distillation of the

alkaloid led to no useful result. Twenty years later, E. Späth and A. Kolbe (3), working with a specimen of Greshoff's material, showed the alkaloid to be 1-methyl-4-quinolone (I). New analyses of the alkaloid indicated the formula $C_{10}H_9ON$, and showed the presence of an *N*-methyl group. By reduction with sodium and alcohol, or better by electrolytic reduction at a lead cathode, an oxygen-free base, $C_{10}H_{13}N$, was obtained, which was identified as 1-methyl-1:2:3:4-tetrahydroquinoline (II) by comparison of its picrate (m.p. 122°) with a synthetic specimen.

The presence of a quinoline nucleus was confirmed by treating the alkaloid with one molecular equivalent of phosphorus pentachloride and excess of phosphorus oxychloride at 150° . When the resulting chlorine containing base (III) was dehalogenated by hydrogenation (Pd/BaSO₄) in acetic acid containing sodium acetate, quinoline was obtained. The base (III) was identified as 4-chloroquinoline (m.p. $26-28^\circ$) by comparison with a synthetic specimen, thus establishing the position of the oxygen atom in the alkaloid.



b. Synthesis. It was shown by M. Conrad and L. Limpach (4) that 4-methoxyquinaldine (IV, R = Me) undergoes rearrangement to 1-methyl-4-quinaldone (V, R = Me) when strongly heated. By applying this method, E. Späth and A. Kolbe (3) converted 4-hydroxyquinoline into 1-methyl-4-quinolone, which was identical in all respects with echinopsine.

Two and one half grams of 4-hydroxyquinoline are warmed with a solution of 0.4 g. of sodium in 8 ml. of methanol until dissolved. After addition of 6 ml. of methyl iodide the mixture is sealed in a Carius tube and heated for 20 hours at 100° . The product, after removal of methanol and methyl iodide, is taken up in water, made strongly alkaline and exhaustively extracted with chloroform. Distillation of the chloroform leaves 1.6 g. of a pale-colored crystalline mass, which after distillation in a vacuum, crystallization from benzene and desiccation has m.p. 152° .

An impure specimen (m.p. 143°) of 1-methyl-4-quinolone had been prepared previously by H. Meyer (5) by heating 4-methoxy-quinoline (IV, R = H) at 300°.

III. The Furoquinoline Group*

1. OCCURRENCE AND ISOLATION

a. Dictamnine. This alkaloid was first isolated from white dittany root (*Dictamnus albus* L.) by H. Thoms (6); other basic constituents identified were choline and trigonelline (7). Later, dictamnine was isolated from the leaves of *Skimmia repens* Nakai, by Y. Asahina, T. Ohta, and M. Inubuse (8), who proved its identity with the dictamnus-root alkaloid and elucidated its structure.

A 5 kg. batch of minced leaves of *Skimmia repens* is thoroughly moistened with 10% aqueous sodium carbonate, and extracted twice by stirring at 50° with 30 l. portions of light petroleum. The combined petroleum extracts are shaken with two 5 l. portions of 5% hydrochloric acid, and the acid solution is washed with ether, basified with sodium carbonate and extracted with chloroform. Evaporation of the chloroform affords the crude alkaloid (average yield, 0.14%) which is purified by crystallization from alcohol.

b. Skimmianine. In 1904, J. Honda (9) isolated from *Skimmia japonica* Thunb., a crystalline alkaloid which he named skimmianine, and which he showed to be the poisonous principle of the plant. It occurs in all parts of the plant but most abundantly in the leaves. The alkaloid was more fully characterized by Y. Asahina and M. Inubuse (10), who elucidated its structure. Subsequently, skimmianine has been isolated from several other rutaceous plants, namely; *Fagara coco* (Gill) Engl. (11) (see below), *Fagara manchurica* Honda (*Zanthoxylum schini-folium* Sieb. et Zucc.) (12), the root-bark of *Fagara zanthoxyloides* Lam. (13), the fruits of *Orixa japonica* Thunb. (14), and the bark of the East Indian satinwood, *Chloroxylon swietenia* D.C. (15).† Extraction of the alkaloid from *Skimmia japonica* leaves is performed by a similar procedure to that described above for dictamnine.

c. γ-Fagarine. The alkaloids of *Fagara coco*, a tree growing in Central and N. Argentina and in Bolivia, were first investigated by G. V. Stuckert (16), who isolated four crystalline bases, which he named α-, β-, γ-, and δ-fagarine. A re-investigation by V. Deulofeu, R. Labriola and J. de Langhe (11) led to the more complete characterization

* See also Addendum, p. 78.

† Skimmianine has also been found in *Glycosmis pentaphylla* (Retz.) Correa (61) and *Flindersia bourjotiana* F. Muell (63).

of three of the bases and to the elucidation of the structures of two of them; β -fagarine was shown to be identical with skimmianine, while γ -fagarine possesses a closely related structure. A structure has also been proposed for α -fagarine (17) but it has recently been shown to be identical with α -allocryptopine (54).

K. K. Chakravarty (18) has shown that the alkaloid "aegelenine" from *Aegle marmelos* Correa (Bihar variety) is identical with γ -fagarine.

Ten kilograms of the leaves and twigs of *Fagara coco* are soaked for 4 days in 60 liters of 10 % hydrochloric acid, and this extraction is twice repeated at 4-day intervals. Evaporation of the combined extracts under vacuum to about 10 l. gives a precipitate which is removed and freed from alkaloids by repeated maceration with 20 % hydrochloric acid. The combined alkaloidal extract is neutralized with dilute caustic soda and extracted with trichloroethylene. The washed extract is evaporated to dryness, the residue is repeatedly extracted with 13 % hydrochloric acid, and the acid solution is neutralized and extracted with chloroform. The residue from evaporation of the washed chloroform extract is again treated with 13 % hydrochloric acid and the acid solution brought to pH 3.5–4.0 when the weaker bases precipitate, and after 24 hours the precipitate is collected and crystallized from alcohol, giving skimmianine (β -fagarine) (13 g.); concentration of the mother liquors gives crude γ -fagarine (m.p. 120–150°), from which the pure alkaloid (6 g.) is obtained by further crystallization from alcohol. When the aqueous acid filtrate is brought to pH 9, exhaustively extracted with chloroform and the extract evaporated, α -fagarine is obtained. Crystallization from alcohol yields 7 g. of the pure alkaloid, m.p. 163° (11).

d. *Acronycidine*. This alkaloid occurs as a minor constituent (0.1–0.2%) in the bark of two Australian Rutaceae, *Acronychia baueri* Schott, and *Melicope fareana* Engl. It is also present in smaller amount in the leaves of the latter together with about 0.3% of skimmianine. The principal alkaloids in each case are *N*-methylacridone derivatives, and these are separated from acronycidine by extraction with chloroform from a solution in 2–5 % hydrochloric acid. The more strongly basic acronycidine remains in the aqueous phase and is precipitated on basification (19).

2. PHYSICAL, CHEMICAL, AND PHYSIOLOGICAL PROPERTIES

All the alkaloids of this group are well crystalline substances. Skimmianine is described as forming pale yellow prisms (10), but the other alkaloids are colorless. The ultraviolet absorption spectra of dictamnine and skimmianine are similar, both showing maxima at 2440 Å. and 3280 Å. In acronycidine these maxima are shifted to 2560 Å. and 3460 Å. (26). The alkaloids are insoluble in water, sparingly soluble

in ether, and readily soluble in chloroform or warm alcohol. They are weak bases giving solutions which are neutral to litmus; their salts are extensively hydrolyzed by water.

The individual alkaloids give the following color and precipitation reactions:

a. *Dictamnine* forms a sparingly soluble chromate when its solution in dilute sulfuric acid is treated with potassium dichromate, and it gives precipitates with the usual alkaloidal reagents. It dissolves to a colorless solution in concentrated sulfuric acid; addition of a crystal of potassium dichromate gives a green color due to its reduction to a chromic salt (6).

b. *Skimmianine* gives a yellow solution in concentrated sulfuric acid (9) with a green fluorescence (15); on addition of potassium chlorate the solution becomes reddish-brown. With formaldehyde and sulfuric acid it gives a yellow color, changing to green on warming (20). With concentrated nitric acid it gives an orange-red color (9, 15, 16), with Erdmann's reagent a pale yellow turning to red and then orange-red (15), with Fröhde's reagent a green to blue color (9, 15) and with Mandelin's reagent a yellow to green color (15). It gives precipitates with the usual alkaloidal reagents (9, 15); that with potassium bismuth iodide is orange, with potassium tri-iodide chocolate brown (15). Auric chloride gives an unstable precipitate (9).

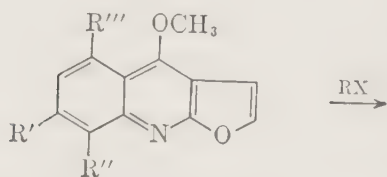
c. γ -*Fagarine* gives no color with concentrated sulfuric acid; with concentrated nitric acid a yellow color is produced. Both Fröhde's and Erdmann's reagents give a greenish-yellow, Mandelin's reagent a pale to deep red (18).

The alkaloids possess toxic properties, but an accurate study of their pharmacology is rendered difficult by the great insolubility of the free bases and the high acidity of solutions of their salts. Thus P. Wolff (21) studied the toxicity of dictamnine hydrochloride, but his findings were criticized by A. Ogata (22) on the ground that the observed effects could be ascribed in part to the acidity alone. A recent account of the pharmacology of dictamnine has been given by V. N. Kovalenko (23). J. Honda (9) described the toxic properties of skimmianine, but his investigations were conducted with rather impure material. The alkaloid "chloroxylonine," isolated from satinwood by S. J. M. Auld (24), which has since been shown to be identical with skimmianine (15), appeared to be responsible for the dermatitic activity of the wood; the purity of Auld's material, however, is open to doubt, and the effect may well be due to an impurity. The pharmacology of acronycidine (26) in the main resembles that of skimmianine.

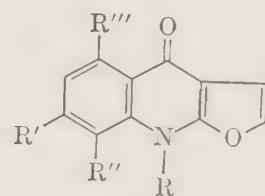
3. DETERMINATION OF STRUCTURE

a. Behavior towards Alkyl and Acyl Halides. The unusual behavior of the alkaloids of this group towards alkyl halides provided an important clue to their structures. Dictamnine (I), which is the simplest member of the group, was the first to be studied. The formula $C_{12}H_{11}O_2N$, proposed by Thoms (6) was corrected to $C_{12}H_9O_2N$ by Asahina, Ohta and Inubuse (8). The substance contains one methoxyl group. It is unaffected by treatment with boiling methyl iodide, but when heated with this reagent in a sealed tube at 80° for 4 hours, it is converted into an isomeric substance, isodictamnine (V) which contains a methylimino group but no methoxyl. If ethyl iodide is used in place of methyl iodide, homoisodictamnine (VI), $C_{13}H_{11}O_2N$, is obtained, which again contains no alkoxy group. These transformations resemble those of the α - and γ -alkoxyquinolines which on heating with alkyl iodides are converted into *N*-alkylquinolones (25).

Dictamnine does not react with acetylating reagents, but when heated with a mixture of benzoyl chloride and benzoic anhydride, it loses methyl chloride and gives benzoylnorisodictamnine (VII). Hydrolysis with alcoholic potash converts this to nordictamnine (VIII) also obtained by demethylation of dictamnine with hot hydrobromic acid.



- I $R' = R'' = R''' = H$
 II $R' = R''' = H; R'' = OMe$
 III $R' = R'' = OMe; R''' = H$
 IV $R' = R'' = R''' = OMe$



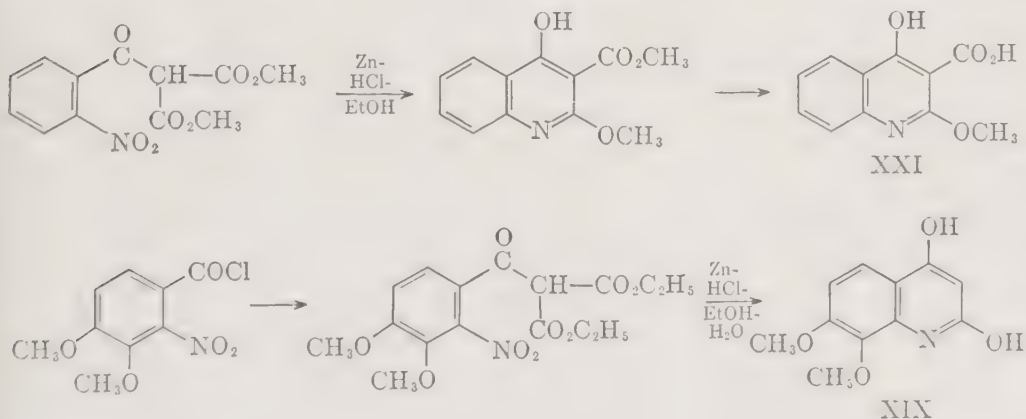
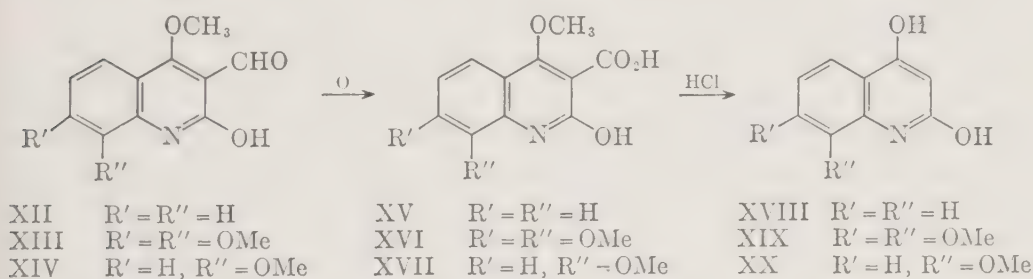
- V $R = Me; R' = R'' = R''' = H$
 VI $R = Et; R' = R'' = R''' = H$
 VII $R = PhCO; R' = R'' = R''' = H$
 VIII $R = R' = R'' = R''' = H$
 IX $R = Me; R' = R''' = H; R'' = OMe$
 X $R = Me; R' = R'' = OMe; R''' = H$
 XI $R = Me; R' = R'' = OH; R''' = H$
 XIa $R = Me; R' = R'' = R''' = OMe$
 XIb $R = H; R' = R'' = R''' = OMe$

γ -Fagarine (II), $C_{13}H_{11}O_3N$, (11) and skimmianine (III), $C_{14}H_{13}O_4N$, (10) contain two and three methoxyl groups respectively, and their molecular formulas correspond to those of a mono- and a di-methoxydictamnine. They are also converted by heating with methyl iodide into isomers (IX, X) containing one methoxyl group less, and a close

relationship in structure is further indicated by the similarity of the ultra-violet absorption spectra of dictamnine and skimmianine (10).

Acronycidine (IV), $C_{15}H_{15}O_5N$, contains four methoxyl groups, and is converted by methyl iodide into isoacronycidine (XIa) (3 methoxyl groups), suggesting that it is a trimethoxydictamnine. One methoxyl group is readily hydrolyzed by hydrochloric acid or alcoholic potash, and the resulting noracronycidine (XIb) gives isoacronycidine on remethylation. The alkaloid can be reduced catalytically to a dihydro derivative (26).

b. Oxidation. On oxidation with potassium permanganate in warm acetone solution, dictamnine loses one carbon atom and is converted into a mixture of an aldehyde, dictamninal (XII), $C_{11}H_9O_3N$, and the corresponding carboxylic acid, dictamninc acid (XV), $C_{11}H_9O_4N$. On heating with concentrated hydrochloric or hydrobromic acid, the acid is demethylated and decarboxylated to give 2:4-dihydroxyquinoline (XVIII). It must therefore be either the 4-hydroxy-2-methoxy- or 2-hydroxy-4-methoxy-derivative of quinoline-3-carboxylic acid. The former compound (XXI) was synthesized from *o*-nitrobenzoic acid by the method of C. A. Bischoff (27) and proved to be different from dictamninc acid, which therefore possesses the latter structure (XV). The



alkaloid is thus recognized as a derivative of 4-methoxyquinoline. Since it is unaffected by acetylating agents and by carbonyl reagents, the second oxygen atom also appears to exist in an ethereal linkage; its position must correspond to that of the hydroxyl group in dictamninc acid, and hence Asahina, Ohta and Inubuse (8) assigned the structure (I) to dictamninc.

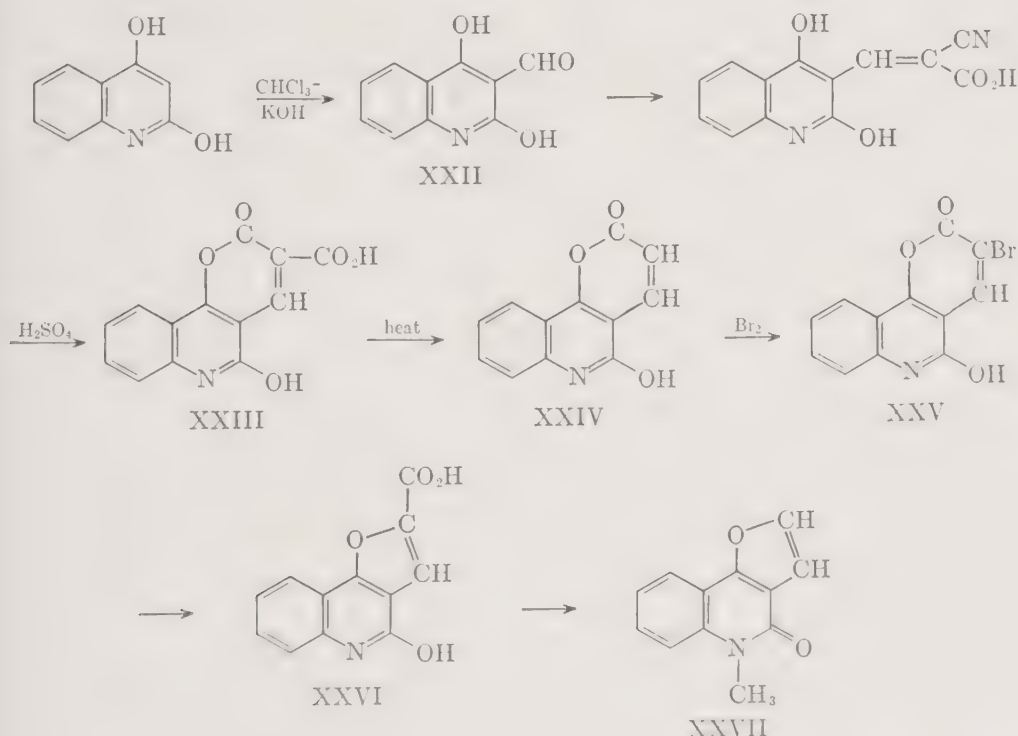
The oxidation of skimmianine (10) and γ -fagarine (11) follows an analogous course. Skimmianine gives rise to skimmianal (XIII) and skimmianic acid (XVI); degradation of the latter with hot concentrated hydrochloric acid leads to a dimethoxy-2:4-dihydroxyquinoline. An indication of the relative positions of the methoxyl groups was obtained when isoskimmianine was demethylated with hydrogen bromide in acetic acid. The resulting phenolic base (XI) showed color reactions of the catechol type. The structure (III) of the alkaloid was finally established by Y. Asahina and S. Nakanishi (28), who synthesized 6:7- and 7:8-dimethoxy-2:4-dihydroxyquinoline and showed the latter (XIX) to be identical with the degradation product of skimmianic acid. 2-Nitro- and 6-nitroveratric acids, prepared from vanillin by the method of R. Pschorr and C. Sumuleanu (29), were separately subjected to the Bischhoff synthesis (27), their chlorides being condensed with diethyl malonate, and the products reduced, cyclized and decarboxylated by treatment with tin and aqueous-alcoholic hydrochloric acid.

By a similar degradation γ -fagarine gives rise to a methoxy-2:4-dihydroxyquinoline, which B. Berinzaghi, A. Muruzabal, R. Labriola and V. Deulofeu (30) showed to be identical with the 8-methoxy isomer (XX) synthesized by Bischhoff's method. γ -Fagarine therefore possesses the structure II.

Acronecydine is also oxidized to an aldehyde and an acid ($C_{14}H_{15}O_7N$); the latter is degraded by hydrochloric acid to a substance, $C_{12}H_{13}O_5N$, which proves to be a dihydroxytrimethoxyquinoline. Nitric acid, or even nitrous acid, converts acronecydine quantitatively into a sparingly soluble, yellow quinone, $C_{13}H_9O_5N$, which contains two methoxyl groups and which has the properties of a *p*-quinone. Thus two of the methoxyl groups of acronecydine are situated at the 5 and 8 positions of the quinoline nucleus, a third must be placed at position 4, and of the remaining positions 6 and 7 the latter is preferred for the fourth methoxyl group, in view of the association of the alkaloid with skimmianine and because noracronecydine couples with diazonium salts. The structure (IV) thus deduced for the alkaloid has been confirmed by the degradation of the dihydroxytrimethoxyquinoline to 2:4:5-trimethoxybenzoic acid, and a number of other reactions of the alkaloid have been described (26).

4. ATTEMPTED SYNTHESIS OF DICTAMNINE: ψ -DICTAMNINE

None of the alkaloids of this group has been synthesized as yet. An attempt by Y. Asahina and M. Inubuse (33) to synthesize dictamnine led to an isomer of the alkaloid, which was named ψ -dictamnine. Dictamninal, which is obtained from the alkaloid most conveniently by ozonolysis, is demethylated by aqueous hydrobromic acid or caustic potash to nordictamninal (XXII), which may also be synthesized from 2:4-dihydroxyquinoline by the Reimer-Tiemann reaction. A coumarin synthesis was carried out on nordictamninal by condensation with cyanoacetic acid followed by hydrolysis and cyclization with sulphuric acid, and decarboxylation of the resulting acid (XXIII) by heat. The product (XXIV) was brominated, and the bromo derivative (XXV) on treatment with aqueous caustic potash underwent ring contraction to the furoquinoline derivative (XXVI), a series of reactions analogous to the conversion of coumarin to coumarilic acid. Since attempted decarboxylation of (XXVI) led to extensive decomposition, the substance was converted into its *N*-methyl derivative. Heating then effected decarboxylation to ψ -dictamnine (XXVII), which, since it is not identical with isodictamnine (V), must be a derivative of (3,2-c)-furoquinoline.



5. TABLE OF PHYSICAL CONSTANTS

TABLE 2

THE FUROQUINOLINE ALKALOIDS AND RELATED PRODUCTS

Compound	M.p., °C.	Crystal Form	References
Dictamnine	132-133	Colorless prisms (C ₂ H ₅ OH)	6, 8
Aurichloride	152	Yellow prisms	6, 7
Chloroplatinate	Sinters 210		6
Hydrochloride	195; 170 (dec)	Colorless needles (C ₂ H ₅ OH)	7, 8
Picrate	163	Yellow prisms (C ₂ H ₅ OH)	8
Picrolonate	178	Yellow	7
Isodictamnine	188	Colorless needles (H ₂ O)	8
Isohomodictamnine, Trihydrate	ca. 80	Colorless needles (C ₂ H ₅ OH-H ₂ O)	8
Hemihydrate	143	(by drying in vacuum desiccator)	8
Anhydrous	ca. 150	(by heating in vacuum)	8
Nordictamnine	249	Colorless needles (C ₂ H ₅ OH-H ₂ O)	8
N-Benzoyl deriv.	165	Colorless needles (C ₂ H ₅ OH)	8
Dictamninal	259-260	Colorless needles (C ₂ H ₅ OH)	8
Phenylhydrazone	228	Yellow needles (C ₂ H ₅ OH)	8
Dictamninc acid	260 (dec)	Colorless needles (AcOH)	8
2:4-Dihydroxyquinoline	>320	Colorless needles (dil. HCl)	8, 31
Nitroso deriv.	208 (dec)	Orange-yellow prisms (C ₂ H ₅ OH)	8, 32
Nordictamninal	>350	Colorless crystals (AcOH)	33
Phenylhydrazone	235	Yellow needles (C ₂ H ₅ OH)	33
ψ-Dictamnine	225	Colorless needles (C ₂ H ₅ OH-H ₂ O)	33
Skimmianine	176	Small pyramids or pale yellow tetragonal prisms (C ₂ H ₅ OH)	9, 10
Chloroplatinate		Orange-yellow, rhombic plates	9, 15
Picrate	195-197 (dec)	Yellow prisms or silky needles (C ₂ H ₅ OH)	10, 15
Isoskimmianine	185	Colorless needles (C ₂ H ₅ OH-H ₂ O)	10
Demethylated Isoskimmianine (XI)	218	Colorless needles (C ₂ H ₅ OH)	10
Diacetyl deriv.	183	White needles (C ₂ H ₅ OH)	10
Skimmianal	238	Colorless needles (C ₂ H ₅ OH)	10, 15
Phenylhydrazone	210	Yellow needles (C ₂ H ₅ OH)	10, 15
Skimmianic acid	248	Colorless needles (AcOH)	10, 15
2:4-Dihydroxy-7:8-dimethoxyquinoline	250	Colorless prisms (C ₂ H ₅ OH-H ₂ O)	10, 28, 15
Nitroso deriv.	247 (dec)	Yellow-red needles (AcOH)	10, 28, 15

TABLE 2 (Continued)

Compound	M.p., °C.	Crystal Form	References
γ -Fagarine	142	Prismatic crystals (C ₂ H ₅ OH)	11
Chloroplatinate	(dec) >200	Orange needles (H ₂ O)	18
Picrate	177	Yellow needles (C ₂ H ₅ OH)	11, 18
Picrolonate	174–175	Yellow needles (C ₂ H ₅ OH)	11
Iso- γ -fagarine	179	Colorless needles (CH ₃ OH)	11
γ -Fagaraldehyde	185	Fine yellow needles (C ₂ H ₅ OH)	11, 18
Phenylhydrazone	207	Yellow needles (C ₂ H ₅ OH)	11, 18
γ -Fagaric acid	215	Colorless needles (acetone)	11, 18
2:4-Dihydroxy-8-methoxyquinoline	250	Long prisms (C ₂ H ₅ OH)	11, 30, 18
Nitroso deriv.	216–217 (dec)	Red needles	11, 30, 18
Acronycidine	*136.5–137.5	Colorless needles or large prisms (C ₂ H ₅ OH)	19
Hydrochloride	*121 (dec)	Pale yellow needles (acetone)	26
Picrate	*181.5–182.5	Long yellow needles (CH ₃ OH)	26
Dihydroacronycidine	*188.5–190.5	Thick white plates (ethyl acetate)	26
Isoacronycidine	*172–173	Long colorless needles (H ₂ O)	26
Hydrochloride	188–190	Yellow needles (acetone)	26
Noraacronycidine (XIb)	*185.5–186.5	Colorless prisms (ethyl acetate)	26
Acetyl-	*133.5–134.5	Colorless needles (C ₂ H ₅ OH)	26
Benzoyl-	*142.5–143.5	Long cream needles (C ₂ H ₅ OH—H ₂ O)	26
Norisoacronycidine (XIa, R''' = OH)	*226–227	Cream needles (CHCl ₃ —C ₂ H ₅ OH)	26
Acetyl-	*174–175	Colorless prisms (xylene)	26
Acronycidinequinone	299–300 (dec)	Yellow needles (AcOH)	26
Diacetyldihydro-	234–235	Colorless needles (CH ₃ OH)	26
Isoacronycidinequinone	*250–251 (dec)	Reddish-orange needles (CH ₃ OH)	26
Noraacronycidinequinone	dec > 245	Orange-red prisms (AcOH)	26
Acronycidaldehyde	*219.5–220.5	Fine cream needles (C ₂ H ₅ OH)	26
2:4-Dinitrophenylhydrazone	302–304 (dec)	Dark red needles (AcOH)	26
Acronycidic acid	*210–212 (dec)	Colorless needles (C ₂ H ₅ OH)	26
2:4-Dihydroxy-5:7:8-trimethoxyquinoline	*231–232	Colorless needles (ethyl acetate-light petroleum)	26
Monoacetyl-	*204–206	Fine white needles (CH ₃ OH—H ₂ O)	26
Nitroso-	*241–243 (dec)	Red needles (AcOH)	26

* Corrected m.p.

6. ADDENDUM

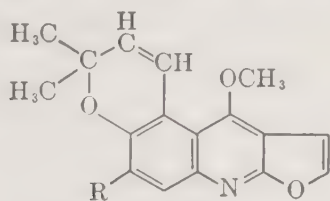
Several new furoquinoline alkaloids have recently been discovered, and elucidation of the structure of the previously known kokusaginine has shown it to belong to this group. All these alkaloids have been isolated from Australian Rutaceae.

a. *Kokusaginine* was first isolated, together with kokusagine, from *Orixa japonica* Thunb. by M. Teresaka (57). It has recently been found in the bark of *Evodia xanthoxyloides* F. Muell (58) and of *Flindersia collina* Bail. (59), and in the leaves of *Acronychia baueri* Schott (60) and of *Glycosmis pentaphylla* (Retz.) Correa (61). It forms colorless prisms, m.p. 171°, and gives a picrate, m.p. 218°, and a sparingly soluble hydrochloride, m.p. 224° (dec). Teresaka (57) established the molecular formula $C_{14}H_{13}O_4N$, showed the presence of three methoxyl groups, and observed the isomerization of the alkaloid by methyl iodide to isokokusaginine (m.p. 249–250°), which contains two methoxyl and one methylimino group. F. A. L. Anet and co-workers (59) oxidized the alkaloid with permanganate and obtained a mixture of an aldehyde and the corresponding acid, $C_{13}H_{13}O_6N$. Treatment of the latter with hydrochloric acid gave 2:4-dihydroxy-6:7-dimethoxyquinoline, identified by comparison with a synthetic specimen (28). Kokusaginine is therefore 6:7-dimethoxydictamnine. *Kokusagine*, $C_{13}H_9O_4N$ (m.p. 201°; picrate, m.p. 178°), which also shows the characteristic behavior of members of this group towards methyl iodide and potassium permanganate, is probably a methylenedioxydictamnine (62).

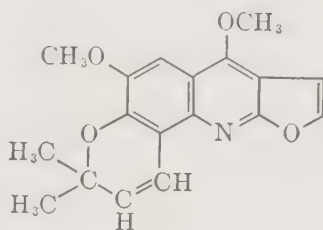
b. *Flindersiamine* occurs with kokusaginine in *Flindersia collina* Bail. (59), and with skimmianine in *Flindersia bourjotiana* F. Muell (63). It forms thick white needles, m.p. 206–207°, from methanol, and small cubes from benzene, and gives a picrate, yellow needles, m.p. 200–201°, from propanol. It has the molecular formula $C_{14}H_{11}O_5N$, contains one methylenedioxy and two methoxyl groups, and resembles the other furoquinoline alkaloids in its ultraviolet absorption spectrum. It is isomerized by methyl iodide to isoflindersiamine, m.p. 209–211°, and on oxidation gives an acid, $C_{13}H_{11}O_7N$, which is converted by boiling dilute hydrochloric acid into 2:4-dihydroxy-8-methoxy-6:7-methylenedioxyquinoline, identified by comparison with a specimen synthesized from myristicin aldehyde. The alkaloid is therefore 8-methoxy-6:7-methylenedioxydictamnine (59).

c. *Acronidine* occurs with skimmianine, acronycidine, and kokusaginine, and four acridone alkaloids (see Vol. II, Chapter XII) in the leaves of *Acronychia baueri*. It forms large, colorless prisms, m.p. 151–153° (picrate, yellow needles, m.p. 216–218° dec), of formula

$C_{18}H_{17}O_4N$, contains two methoxyl but no methylimino groups, and is isomerized by methyl iodide at 100° to isoacronidine, m.p. $231-232^\circ$. Aleoholic hydrochloric acid partially demethylates acronidine to noracronidine, m.p. $256-257^\circ$, containing one methoxyl and one phenolic hydroxyl group, which is degraded by boiling 30% potassium hydroxide solution with liberation of approximately equimolecular proportions of acetaldehyde and acetone; methylation of the alkaline reaction mixture gives isokokusaginine. Oxidation of acronidine with permanganate yields α -hydroxyisobutyric acid. It is deduced (60) that acronidine contains a 2:2-dimethylpyran ring fused to the quinoline ring and that its structure is either AI ($R = CH_3O$) or AII. [Compare the structure of the accom-



AI



AII

panying acridone alkaloid, acronycine (Volume II, p. 365).] In support of this view, the alkaloid is found to be hydrogenated to a tetrahydro derivative; a "hexahydro" compound which is also formed has the properties of an α -quinolone and must arise by hydrogenolysis of the furan ring (60).

d. *Medicosmine* has been isolated from the bark of *Medicosma cunninghamii* Hook. as almost colorless needles, m.p. $138.5-139.5^\circ$ (picrate, fine yellow needles, m.p. $190-191^\circ$). It has the formula $C_{17}H_{15}O_3N$, contains one methoxyl group, and is isomerized by methyl iodide to isomedicosmine (cream prisms, m.p. $226-227^\circ$). Aleoholic hydrochloric acid demethylates it to normedicosmine (pale yellow prisms, m.p. 210° ; acetyl derivative, colorless flat needles, m.p. $184-185^\circ$). Permanganate oxidation, as in the case of acronidine, gives α -hydroxyisobutyric acid, and alkaline degradation of normedicosmine gives acetaldehyde, acetone, and, after methylation of the alkali-soluble product, a substance, $C_{13}H_{11}O_3N$ (colorless needles, m.p. $215-216^\circ$), containing one methoxyl and one methylimino group. Oxidation of this substance with permanganate gives 6-methoxy-4-hydroxy-1-methyl-2-quinolone, identified by comparison with a synthetic specimen. Medicosmine is accordingly formulated (60) either as AI ($R = H$) or as the isomer having linear fusion of the pyran ring. On hydrogenation, it behaves like acronidine, giving a tetrahydro and a "hexahydro" derivative.

IV. Alkaloids of Angostura Bark

1. OCCURRENCE AND ISOLATION

Angostura bark is native to South America where it has long been used in the treatment of fevers. It was brought to Europe around the end of the 18th century, and for some time enjoyed an apparently undeserved reputation as a febrifuge. Cases of poisoning, caused by adulteration with *Strychnos* bark, eventually brought the drug into disrepute, however, and its use in medicine was largely abandoned. It is now used principally as a tonic and in the compounding of aperitifs, in consequence of its content of bitter principles. The alkaloids of the bark are usually considered to possess no appreciable pharmacological activity, but Raymond-Hamet (52) has ascribed to cusparine a "sympathicosthenic" action, that is, it increases the sensitivity of the sympathetic nervous system to stimulation.

Genuine Angostura bark is derived from *Galipea officinalis* Hancock (syn., *Cusparia trifoliata* Engl.). The first chemical study of the material was made by Oberlin and Schlagdenhauffen (34), who investigated its content of essential oil. The presence of alkaloids was first observed by Körner and C. Böhringer (35), who in 1883 isolated the two principal crystalline alkaloids, cusparine, $C_{19}H_{17}O_3N$, and galipine, $C_{20}H_{21}O_3N$, which were characterized by the preparation of various salts; the presence of a third crystalline alkaloid (m.p. 180°) was also recorded. The total alkaloid content of the bark was estimated at 0.8–1%.

A more exhaustive investigation of the alkaloids of Angostura was undertaken by H. Beckurts, and continued by his pupil J. Tröger. H. Beckurts and P. Nehring (36) claimed to have isolated, in addition to cusparine and galipine, two new alkaloids which they named cusparidine and galipidine, but these were subsequently shown (41) to be impure samples of the two principal bases. H. Beckurts and G. Frerichs (38) described a more weakly basic alkaloid, cuspareine, $C_{18}H_{19}O_2N$ (40), whilst J. Tröger and O. Müller (39) added a fourth alkaloid, galipoidine, $C_{19}H_{15}O_4N$ (40). In addition to these crystalline alkaloids, the extract of the bark contains a large quantity of amorphous and oily basic material. Several more alkaloids were isolated from the latter by E. Späth and his collaborators. Treatment of the total alkaloid extract with aqueous sodium hydroxide gave a phenolic fraction (46) from which Späth and G. Papaioanou (47) isolated a new crystalline alkaloid, galipoline, $C_{19}H_{19}O_3N$. The nonphenolic portion, after the removal of cusparine and galipine, was a mixture of liquid bases from which Späth and J. Píkl (48, 49) separated quinoline, quinaldine, 2-*n*-amylquinoline, 4-methoxy-2-*n*-amylquinoline and 1-methyl-2-quinolone.

Körner and Böhrlinger (35) isolated the alkaloids from the bark by direct extraction with ether. The crude mixture of bases was treated with oxalic or sulphuric acid, when cusparine oxalate or sulphate crystallized; galipine was obtained by crystallization of the base recovered from the mother liquors. The methods of separation used by Beckurts and Nehring (36), Beckurts and Frerichs (38) and Tröger and O. Müller (39) were tedious and unsatisfactory, and Tröger and W. Kroseberg (41) recommended the original oxalate separation. A further improvement was effected by Späth and H. Eberstaller (46), who showed that extraction of the alkaloids from the bark by ether is incomplete since, contrary to the statement of Körner and Böhrlinger (35), they are present in the bark partially in the form of salts. By extraction with alcohol, the yield of alkaloids is markedly increased.

The powdered bark, in 300-g. portions, is extracted with alcohol in a Soxhlet apparatus for 24 hours. The extract from one kilogram of bark is concentrated under reduced pressure to a thick sirup and shaken for some hours with 25 % sodium hydroxide solution, until most of the black impurities have dissolved. The alkaline extract is reserved for the isolation of galipoline, and the undissolved alkaloids are exhaustively extracted with ether. The washed and filtered ethereal solution is shaken with successive 200-ml. portions of 1 % hydrochloric acid as long as appreciable quantities of alkaloid are extracted.

The major part of the alkaloid mixture separates as a yellowish, sparingly soluble hydrochloride. This is separated into cusparine and galipine by conversion to the oxalate. The sparingly soluble cusparine oxalate is purified by crystallization from saturated aqueous oxalic acid, and the regenerated base is crystallized to constant melting point from light petroleum; yield, 10.6 g. Crude galipine is precipitated on basification of the soluble oxalates, and is purified by repeated crystallization from light petroleum; the yield is 3.5 g., but a considerable amount of galipine is lost in the hydrochloric acid mother liquors (46).

Basification of the hydrochloric acid mother liquors derived from the extraction of 16 kg. of bark gives 200 g. of an oily mixture of bases, which is shaken repeatedly with light petroleum. The extract contains about 30 g. of oil which is distilled in superheated steam and then fractionated at 14 mm. pressure, three fractions boiling over the ranges 100–145°, 145–190° and 190–200° being collected. The third fraction (8.7 g.) consists largely of 4-methoxy-2-*n*-amylquinoline, which is purified by removal of a little non-basic material and re-fractionation (48). The first fraction is distilled in steam until 150 cc. of distillate have been collected, and the bases recovered from the distillate by ether extraction are fractionated at 10 mm., giving quinoline and quinaldine (combined yield, about 0.003 % of dry bark). The remaining material from fraction 1, combined with fraction 2, is extracted twice with boiling water. The extract, after making strongly alkaline, yields to ether 0.6 g. of a base which on treatment with 13 % hydrochloric acid gives a crystalline hydrochloride. Basification of the recrystallized hydrochloride gives 1-methyl-2-quinolone which is purified by distillation at 130–140° (bath) /0.3 mm. (yield, about 0.01 % of dry bark).

The water insoluble bases, together with those recovered from the mother liquors of the 1-methyl-2-quinolone hydrochloride, are heated with 40 cc. of fuming hydrochloric acid in a sealed tube at 175° for 2.5 hours, whereby the 4-methoxy-2-*n*-amyl-

quinoline is demethylated. The dark solution is diluted with water, filtered from tarry material, neutralized with sodium bicarbonate and continuously extracted with ether. 4-Hydroxy-2-*n*-amylquinoline crystallizes from the extract and is removed by filtration. The filtrate is evaporated and distilled at 14 mm. The fraction boiling at 130–170°, which contains 2-*n*-amylquinoline, is heated with excess of methyl iodide and anhydrous ether for 3 days at 100° in a sealed tube. The methiodide thus produced is collected and decomposed by distillation at 10 mm., and the distillate is fractionated, the 2-*n*-amylquinoline boiling at 130–145°/10 mm. (yield, about 0.003 %) (49).

For the isolation of galipoline, the alkaline extract of the crude alkaloids is poured into 5 % hydrochloric acid with stirring, and the tarry precipitate is extracted several times with boiling water. The aqueous extract is washed with chloroform, made alkaline with sodium carbonate, filtered to remove a precipitate and extracted with chloroform. The residue remaining after evaporation of the chloroform is treated with 5 % caustic soda solution, undissolved material is removed and the solution is neutralized with carbon dioxide. The precipitate (3 g. from 16 kg. bark) is further purified by extraction with ether; the crystals which separate from the ethereal extract are recrystallized from water (47).

Cuspareine and galipoidine, which were not obtained by the above extraction procedure, were isolated by J. Tröger and O. Müller (39) as follows:

The crude total alkaloids (1 kg.) are dissolved in ether (1 liter) and extracted with 20 % acetic acid until the extract is only pale yellow. Sufficient concentrated sulphuric acid is added to the extract to precipitate completely a deep yellow, sparingly soluble sulfate, which is collected and washed with water, alcohol and ether. The free bases are liberated by treatment with ammonia and crystallized several times from alcohol, giving reddish-white crystals (140 g.), m.p. 95°. On treatment with ligroin a soluble portion, consisting chiefly of cusparine, and an insoluble portion are obtained. The latter contains a fraction which is sparingly soluble in alcohol, and on recrystallization from a large volume of alcohol this fraction yields galipoidine. A further quantity can be obtained by concentration of the alcoholic solutions and precipitation with benzene, in which the alkaloid is insoluble.

Further extraction of the ethereal solution with dilute sulphuric acid removes a mixture of weaker bases, which on precipitation with ammonia is obtained as a thick, dark reddish-brown oil. This is extracted twice with hot ligroin. On thorough cooling the extract deposits cuspareine as white needles, and an additional quantity can be obtained by concentrating the mother liquor. After washing with cold alcohol to remove adherent oil, the alkaloid is recrystallized from hot alcohol.

2. PHYSICAL AND CHEMICAL PROPERTIES; COLOR AND PRECIPITATION REACTIONS

a. Cusparine forms colorless prismatic crystals, m.p. 92°, belonging to the monoclinic system; crystallographic examination by M. de Angelis (51) gave axial ratios, $a:b:c = 1.2496:1:1.1678$, $\beta = 69^\circ 49'$. A second crystalline form, thick amber-colored crystals, m.p. 110–122°, was described by J. Tröger and H. Runne (40), while Tröger and W. Beck (42) claimed the existence of a third modification, long glistening straw-

yellow needles, m.p. 91–92°. When pure, the alkaloid gives colorless salts (35, 38); owing to the great difficulty of effecting complete purification, however, most of the salts have been described as yellow. The oxalate, sulfate and hydrochloride are sparingly soluble in water. The alkaloid is optically inactive.

Cusparine gives a dull red color, changing to cherry-red when added to sulfuric acid. After 10 minutes a greenish-yellow layer appears and gradually spreads through the liquid (36). With sulfuric acid and titanium dioxide, or with sulfuric acid and furfural, a reddish-brown color develops. The alkaloid gives a yellow solution in fuming nitric acid; evaporation and treatment of the residue with caustic potash gives an orange color. Fröhde's reagent gives a brown solution, changing through violet and bluish-green to a deep blue (37).

White precipitates are formed when a 1% solution of cusparine is treated with phosphotungstic, phosphomolybdic or tannic acids, or with mercuric chloride or potassium mercuri-iodide. Picric acid, platinum chloride or potassium chromate give yellow precipitates, auric chloride or potassium bismuth iodide brown, and potassium ferrocyanide bluish-white (36). By treating a solution of cusparine hydrobromide with bromine water, a series of bromocusparine polybromides is obtained (38).

b. Galipine also forms colorless crystals, and is optically inactive. Although it was originally described as forming intensely yellow salts, Tröger and W. Kroseberg (41) showed that the salts are colorless when rigorously pure. The oxalate, unlike that of cusparine, is very soluble in water and has not been crystallized. The sulfate and the hydrochloride are somewhat more soluble than the corresponding cusparine salts. Galipine gives yellow precipitates with those reagents which give white or yellow precipitates with cusparine; auric chloride or potassium bismuth iodide gives a brown, and potassium ferrocyanide a bluish-white precipitate (36).

c. Cuspareine is optically active, $[\alpha]_D^{20} - 20.4^\circ$ ($C = 6.8$ in ethanol) (55). It has very weakly basic properties. Although soluble in 10% hydrochloric acid, it can be completely extracted therefrom with ether, and no crystalline salts have been obtained (38). It does, however, form a crystalline methiodide when treated with methyl iodide in methanol at 100° (40). The alkaloid is very stable to heat, and can be distilled at 300° under atmospheric pressure with little decomposition. When its solution in dilute sulphuric acid is treated with a trace of an oxidizing agent such as ferric chloride, potassium permanganate or potassium dichromate it becomes deep red and slowly deposits a red, tarry dyestuff. A similar change is brought about by very dilute nitric acid (38), or by boiling dilute hydrochloric acid (55).

d. Galipoidine is colorless, but gives a fluorescent solution in alcohol. It is almost insoluble in benzene and light petroleum. It is basic, and gives a crystalline chloroplatinate and aurichloride; the latter has an abnormal composition, $B_2 \cdot HCl \cdot H AuCl_4 \cdot 1\frac{1}{2} H_2O$ (40).

e. Minor Bases. Of the minor basic constituents isolated by Späth and his collaborators, only galipoline and 1-methyl-2-quinolone are crystalline. Quinoline and quinaldine were characterized by their picrates and their trinitro-*m*-cresolates, and the other bases by their picrates.

3. DETERMINATION OF STRUCTURE

a. Degradation of Cusparine. The molecular formula $C_{19}H_{17}O_3N$ was assigned to cusparine by Körner and Böhringer (35), and was confirmed by Tröger and W. Beck (42), who disproved the alternative formula $C_{20}H_{19}O_3N$ proposed by Beckurts and Nehring (36). Cusparine contains one methoxyl group and no hydroxyl or methylimino groups (38). It is a tertiary base and gives a crystalline methiodide when heated with methyl iodide at 100° for three hours (36). When this salt is treated with caustic potash it gives, not methylcusparine as supposed by Beckurts (37), but isocusparine. This contains an *N*-methyl in place of the *O*-methyl group of cusparine. The isomerization can also be accomplished by heating cusparine at 120 – 190° in methyl iodide vapor (43), by heating cusparine methiodide to 196° (43), or by treating cusparine ethiodide or *n*-propiodide with caustic potash (42).

Cusparine is heated gradually in a stream of methyl iodide vapor. The base melts at 93° , and shows no further change until the temperature reaches 120° , when a pale yellow solid product is obtained. The temperature is then gradually raised until at 191° fusion again occurs. After cooling, the product is crystallized from alcohol, giving isocusparine as colorless needles, m.p. 193 – 194° , free from halogen; yield 90 %.

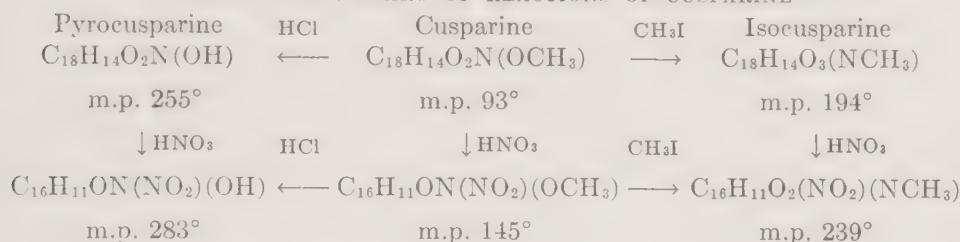
When cusparine is heated alone, or preferably in admixture with urea, at 210 – 220° it is demethylated to pyrocusparine, $C_{18}H_{15}O_3N$ (38). The same reaction occurs when a salt of cusparine with an organic acid is fused (42), or when cusparine is heated in a stream of hydrogen chloride (43). Pyrocusparine contains no methoxyl group and shows cryptophenolic properties; although insoluble in aqueous alkali it readily dissolves in alcoholic potassium hydroxide (42). Zinc dust distillation of cusparine produces pyridine (39). On fusion with caustic potash, protocatechuic acid is formed (38, 39, 35).

When cusparine is treated with nitric acid, it appears to undergo both nitration and degradation. According to Tröger and H. Runne (40), the product has the composition $C_{17}H_{14}O_4N_2$, corresponding to the replacement of a hydrogen atom by a nitro group, and the loss of a portion C_2H_2O (42). The formula for this nitro compound is based on the

analysis of numerous salts. Moreover, nitration of pyroculusparine and isoculusparine gives products of corresponding compositions, which can also be obtained from "nitroculusparine" by demethylation and isomerization respectively (43) (see Chart I). This reaction with nitric acid remains unexplained on the basis of the subsequently established constitution of cusparine (VIII), and appears to require re-investigation.

CHART I

SCHEMATIC SUMMARY OF REACTIONS OF CUSPARINE



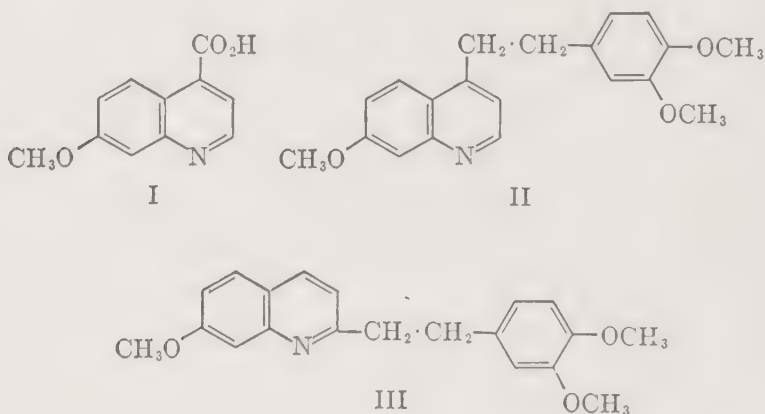
Cusparine is resistant to oxidation by chromic acid and unsatisfactory results are obtained with potassium permanganate, but it can be degraded by prolonged heating with dilute nitric acid (*d.*, 1.075) (42). The "nitroculusparine" first formed is oxidized to an acid, $C_{10}H_7O_3N \cdot H_2O$, which loses its water of crystallization at 140°, and melts with evolution of carbon dioxide at 271–272°. It is recognized as a hydroxyquinoline carboxylic acid by its conversion to quinoline on zinc dust distillation, and its behavior on heating resembles that of kynurenic acid (4-hydroxyquinoline-2-carboxylic acid). The hydroxyquinoline formed by decarboxylation gives a chloroplatinate, yellow-red branching crystals, which sinters at 210° and decomposes at 220°.

b. Degradation of Galipine. Galipine has the molecular formula $C_{20}H_{21}O_3N$ (35, 44) and it contains three methoxyl groups but no methylimino group (39). It is a tertiary base which reacts rather slowly with methyl iodide; when the methiodide is treated with alkali, or when the alkaloid is heated in methyl iodide vapor at 130–190°, isogalipine is formed. This isomerization, like that of cusparine, involves the transfer of a methyl group from oxygen to nitrogen, since isogalipine contains two methoxyl groups and one methylimino group (44). Zinc dust distillation of galipine yields quinoline (41); on alkali fusion, protocatchuic acid is formed (38).

Attempts to oxidize galipine with hot dilute or concentrated nitric acid lead only to a mononitro derivative, $C_{20}H_{20}O_5N_2$, which is very stable to oxidation (41). From the chromic acid oxidation of galipine, Tröger and O. Müller (39) isolated veratric acid and anisic acids. When galipine sulfate is oxidized with potassium permanganate, veratric acid is again obtained, together with an acid, $C_{11}H_9O_3N \cdot 2H_2O$ (m.p. 188–189°;

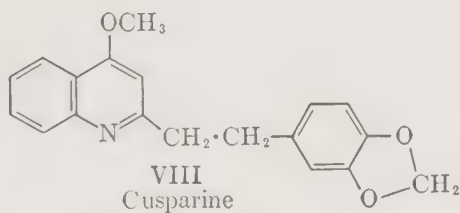
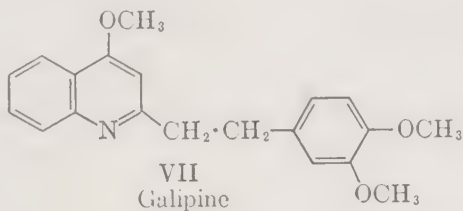
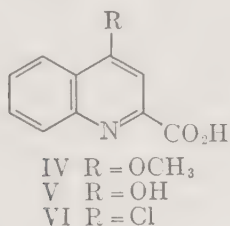
anhydrous, m.p. 194°), which contains one methoxyl group (41). These two products together account for all the carbon atoms and methoxyl groups of the original alkaloid, which the zinc dust distillation suggests to be a quinoline derivative. The acid, $C_{11}H_9O_3N$, should therefore be a methoxyquinoline carboxylic acid. It is decarboxylated to a base (chloroplatinate, m.p. 221°) for which Tröger and Kroseberg (41), in view of the isolation of anisic acid as an oxidation product, suggested the structure 7-methoxyquinoline. Demethylation of the acid gives a hydroxy acid (m.p. 273° on rapid heating, 263° on slow heating) which is probably identical with the hydroxyquinoline carboxylic acid obtained from cusparine. Chromic acid oxidation of the methoxyquinoline carboxylic acid (41), and more vigorous permanganate oxidation of galipine (39) both lead to acids of m.p. 263 – 264° , which are probably both identical with the hydroxy acid, m.p. 273° ; comparison is rendered difficult by the variation of melting point with the conditions of heating.

The vigorous permanganate oxidation of galipine also gives a second nitrogenous acid, m.p. 244 – 246° , (39) which Tröger and Kroseberg supposed to be pyridine-2:3:4-tricarboxylic acid (m.p. 249 – 250°), and on this basis they proposed the structure (I) for the methoxyquinoline carboxylic acid, and (II) for the alkaloid. These structures were disproved by E. Späth and O. Brunner (45), who synthesized the substance (II), and also its isomer (III), but found that neither substance was identical with galipine. Moreover, neither 7-methoxyquinoline-4-carboxylic acid (I) nor the -2-carboxylic acid was identical with the oxidation product $C_{11}H_9O_3N$.



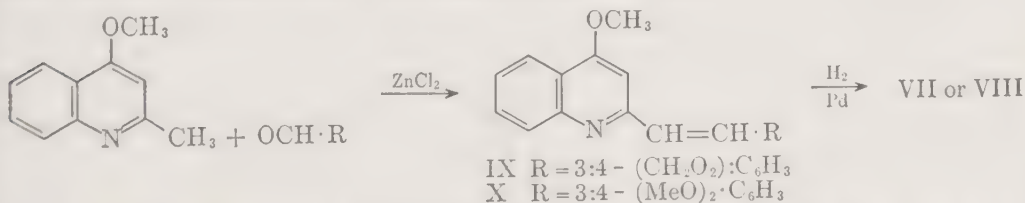
In seeking a further clue to the structure of the alkaloids, Späth and Brunner recognized the significance of the isomerization of cusparine and galipine by methyl iodide. This type of rearrangement is characteristic of 2- and 4-methoxyquinolines (4, 25). The oxidation product of galipine was not identical with the known 2-methoxyquinoline-4-

carboxylic acid, but 4-methoxyquinoline-2-carboxylic acid (IV) synthesized from kynurenic acid (V) by way of the 4-chloro acid (VI), proved to be identical in melting point (194°) and other properties with the degradation acid. In addition, the hydroxyquinolinecarboxylic acid was identified with kynurenic acid (V), by comparison of the methyl esters (m.p. 217°).



Galipine may therefore be assigned the structure (VII), which Späth and H. Eberstaller (46) confirmed by synthesis (see below). Since cusparine resembles galipine in its reactions, and also gives rise to kynurenic acid on degradation, it must be closely related in structure. The formulas of the alkaloids differ by CH₄, and cusparine contains only one methoxyl group, but gives protocatechuic acid on alkali fusion. Späth and Brunner therefore assigned to cusparine the structure (VIII), in which two methoxyl groups of galipine are replaced by a methylenedioxy group, and they confirmed this structure by synthesis.

c. Synthesis of Cusparine and Galipine. 4-Methoxy-2-methylquinoline (4) condenses with piperonal or veratraldehyde in the presence of zinc chloride to give dehydrocusparine (IX) or dehydrogalipine (X) respectively. When these bases, which form bright orange-yellow salts, are reduced catalytically, the alkaloids are obtained (45, 46).



A mixture of 4 g. of 4-methoxyquinoline, 3.6 g. of piperonal and 1.25 g. of anhydrous zinc chloride is heated in an oil bath at 125° , and the water produced is removed every 20 minutes by evacuating the vessel and heating at 100° . When no more water is formed, the cooled mixture is extracted with methanol and the filtered

solution added to dilute hydrochloric acid, when dehydrocusparine hydrochloride is precipitated as orange-yellow needles; yield 5.2 g.

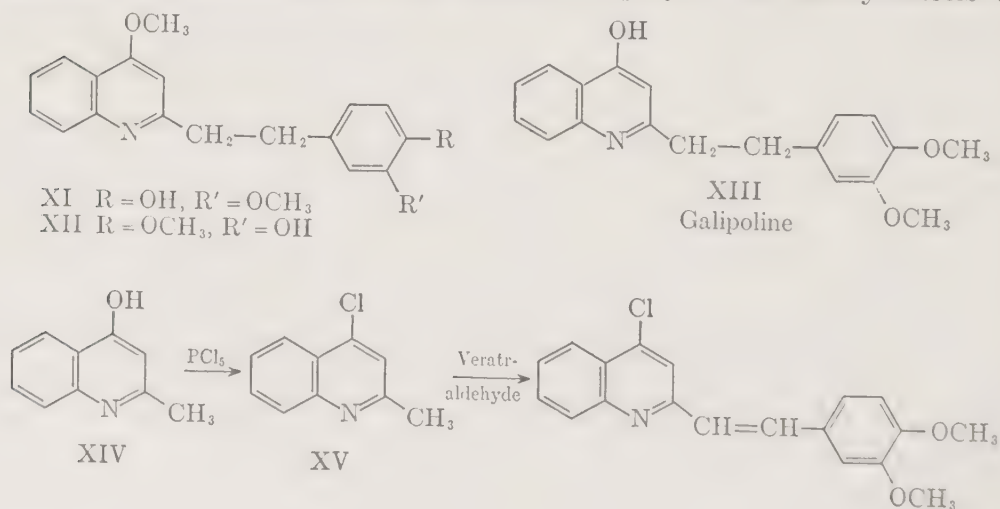
A solution of 1.8 g. of the free base in 10 cc. of 50 % aqueous acetic acid is reduced catalytically until the solution is decolorized. After removal of the catalyst the solution is made alkaline and extracted with ether. The base obtained from this extract is dissolved in hot dilute hydrochloric acid, and on cooling the hydrochloride separates as fine, white needles. The free base is regenerated from this salt and is crystallized from light petroleum.

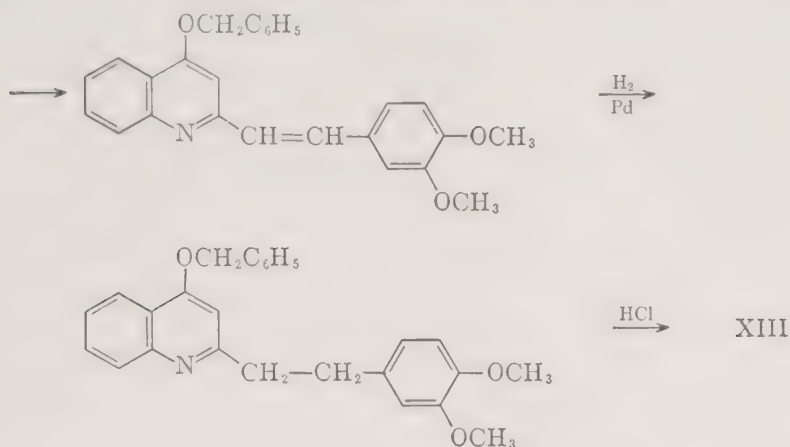
A comparison of the melting points of the natural and synthetic alkaloids and their derivatives is shown in Table 3 (45, 46).

TABLE 3
PHYSICAL PROPERTIES OF NATURAL AND SYNTHETIC BASES

Compound	Synthetic, m.p. °C.	Natural, m.p. °C.	Mixed m.p. °C.
Cusparine	91.5-92	91-92	91-92
Hydrochloride			
Rapid heating	185-187	183-184	185-186
Slow heating	193-194	189-191	190-193
Oxalate (decomp. point)	152-156	155-158	153-158
Isocusparine	193-194	190-191	192-193
Galipine	113.5	113.5	113.5
Hydrochloride	165	165	165
Picrate	194	194	194
Isogalipine	165	165	165

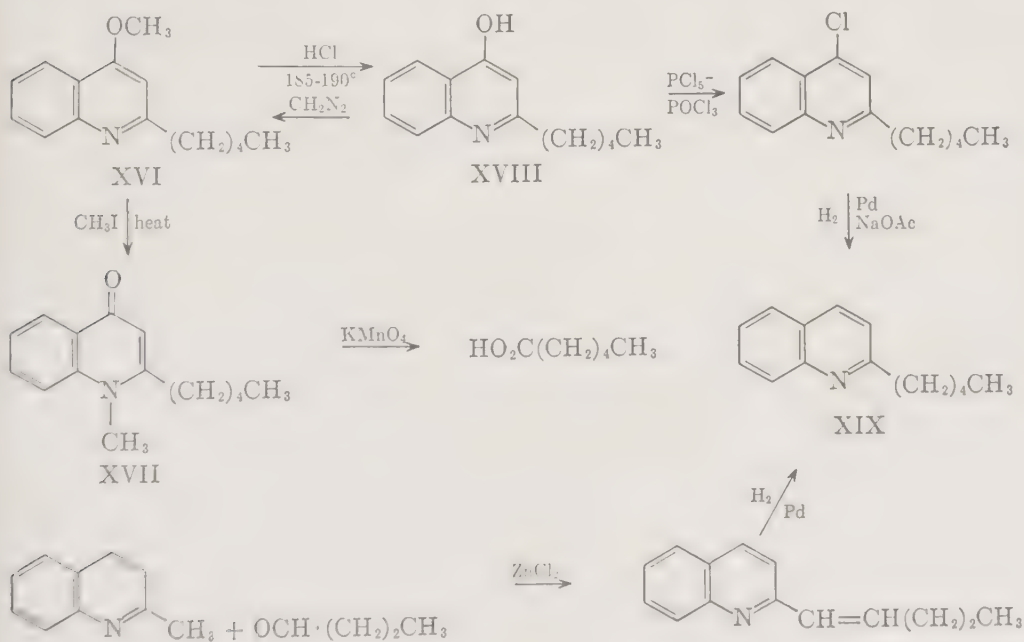
d. Galipoline. This alkaloid, $C_{19}H_{19}O_3N$, contains two methoxyl groups and one phenolic hydroxyl group; on methylation with diazomethane it yields galipine. There are thus three possible structures (XI, XII, XIII) for galipoline, and decision between them was made by synthesis (47). Substances (XI) and (XII) were synthesized from vanillin and isovanillin by the method employed for the synthesis of





galipine, and neither of them was identical with galipoline. The alkaloid therefore has the structure (XIII), and it was synthesized by a modification of the foregoing method. 4-Hydroxy-2-methylquinoline (XIV) fails to condense with veratraldehyde, but the corresponding 4-chloro compound (XV) undergoes the required condensation. Replacement of the chlorine atom in the condensation product by a benzyloxy group is followed by hydrogenation of the ethylenic link, and finally the protecting benzyl group is removed by hydrolysis with hydrochloric acid.

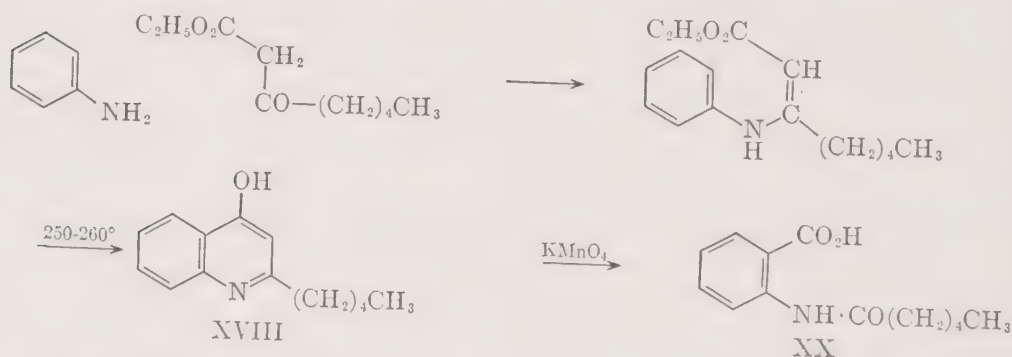
*e. 4-Methoxy-2-*n*-amylquinoline and 2-*n*-Amylquinoline.* The liquid base, $\text{C}_{15}\text{H}_{19}\text{ON}$, b.p. $190\text{--}200^\circ/14\text{ mm.}$, was identified as 4-methoxy-2-*n*-amylquinoline (XVI) by degradation, and then confirmed by synthesis (48). The substance contains one methoxyl group, and forms a meth-



iodide which on distillation loses methyl iodide generating a crystalline, isomeric base (XVII) devoid of methoxyl groups, thus indicating that the alkaloid is a derivative of 4- (or 2-) methoxyquinoline. Oxidation of the isomeric base with potassium permanganate produces *n*-caproic acid, showing the presence of a *n*-amyl side-chain.

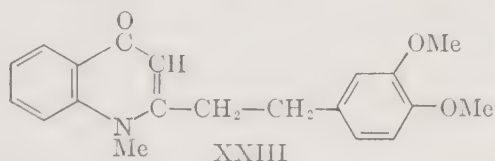
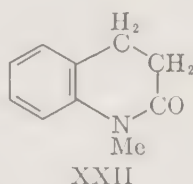
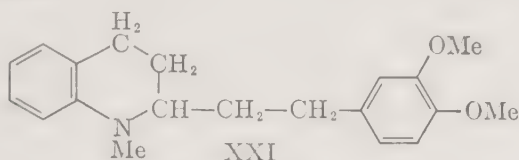
The alkaloid is demethylated by fuming hydrochloric acid at 185–190° to a crystalline, phenolic base (XVIII), which is reconverted to the alkaloid by methylation with diazomethane. Elimination of the hydroxyl group of (XVIII) was achieved by the normal procedure of replacement by halogen followed by catalytic reduction, and the resulting base, $C_{14}H_{17}N$, was identified with a specimen of 2-*n*-amylquinoline (XIX) synthesized from quinaldine and *n*-butyraldehyde. This synthetic base was also identical with the amylquinoline, b.p. 130–145°/10 mm., isolated from *Angostura* bark.

The synthesis of the alkaloid (XVI) was accomplished by the method of Conrad and Limpach (4). Condensation of ethyl caproylacetate with aniline gives the phenolic base (XVIII), identical with that obtained from the alkaloid, and methylation with diazomethane completes the synthesis. Comparison of the natural and synthetic bases was made through the picrates and chloroplatinates, and by isomerization to (XVII). The orientation of the substituents in the synthetic product was confirmed by the oxidation of (XVIII) with alkaline permanganate to *N*-caproylantranilic acid (XX).

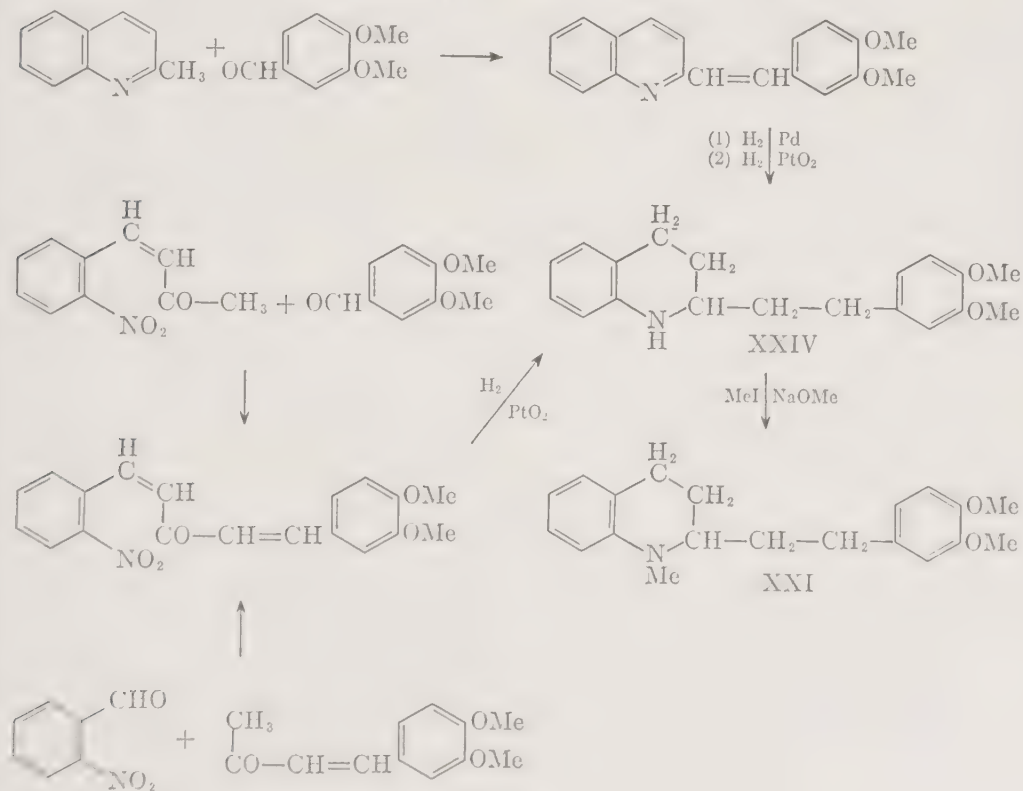


f. Cuspareine and Galipoidine. The constitution of cuspareine (XXI) has been determined by J. Schläger and W. Leeb (55). Fresh analyses showed the older formula, $C_{18}H_{19}O_2N$, of Tröger and Runne (40) to be incorrect, and indicated the base to be either $C_{19}H_{23}O_2N$ or $C_{20}H_{25}O_2N$; degradation shows the latter to be correct. The substance contains two methoxyl groups (40, 56) and one methylimino group (56); on zinc dust distillation it gives quinoline (40). Cuspareine is regenerated when its methiodide is heated with alkali, suggesting that it is not a 4-methoxyquinoline (compare p. 84) (40). On oxidation with potassium permanganate in hot acetone it gives veratric acid and a neutral

oil which consists largely of 1-methyl-1:2:3:4-tetrahydroquinolone-2 (*N*-methyl-dihydrocarbostyryl) (XXII), since on dehydrogenation it yields *N*-methylecarbostyryl (55). Cuspareine is converted by gentle oxidation with permanganate in cold acetone into isogalipine (XXIII), thus confirming its structural relationship to the other Angostura alkaloids.



The constitution (XXI) was confirmed by a synthesis of *dl*-cuspareine, which was identical with the alkaloid in boiling point, in ultra-violet absorption spectrum, and in its sensitivity to hot mineral acid which caused reddening and resinification. *dl*-Norcuspareine (XXIV) was formed by the catalytic reduction of the products obtained by the condensation of veratric aldehyde with quinaldine or with *o*-nitrobenzaldehyde, or of *o*-nitrobenzaldehyde with veratraldehyde, and on methyla-



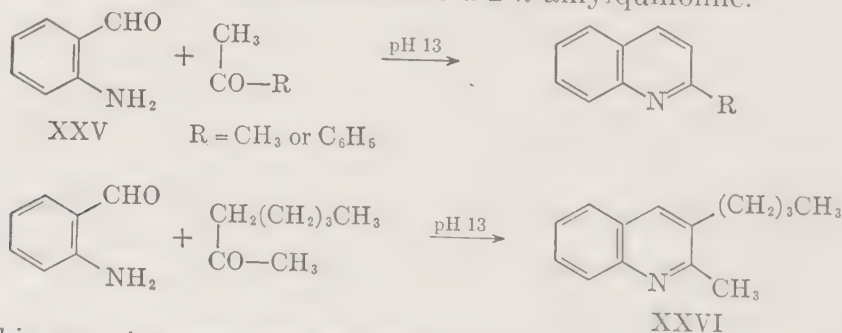
tion with methyl iodide and sodium methoxide *dl*-cuspareine was obtained. Attempts to resolve the base were unsuccessful, since it formed no salts with weak acids, and was resinified by strong acids.

Galipoidine, $C_{19}H_{15}O_4N$ (40), was obtained in only small amount by Tröger and O. Müller (39), while Späth and Eberstaller (46) did not observe its occurrence. Nothing is known of its structure.

4. BIOGENESIS OF THE ANGOSTURA ALKALOIDS

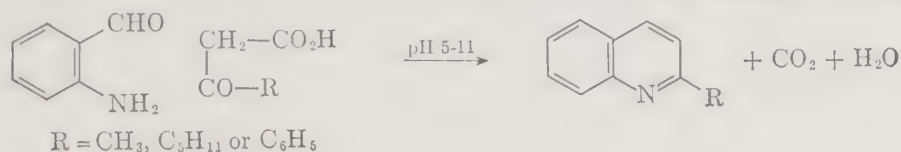
The alkaloids of Angostura form a series whose structural inter-relationships are of particular interest from the biogenetic standpoint. Späth and Pikl (48) commented on the relationship of 4-methoxy-2-*n*-amylquinoline to cusparine, galipine, and galipoline, pointing out that all these alkaloids are quinolines oxygenated at the 4-position, but that they are substituted at the 2-position by two different kinds of groups. They suggested that the alkaloids arose in the plant from a common aromatic precursor, probably an anthranilic acid derivative.

This idea was pursued further by C. Schöpf and G. Lehmann (50), who made the Angostura alkaloids the subject of the first of a series of studies on "organic chemistry under physiological conditions." They considered anthranilic acid itself insufficiently reactive to be a likely starting material, and chose the related aldehyde, *o*-aminobenzaldehyde (XXV), as the most probable aromatic precursor. This aldehyde condenses with methyl ketones to give quinoline derivatives (Friedländer's synthesis), and the ketones which would be required for the production of the Angostura alkaloids are known to occur in plants. A study of Friedländer's synthesis in dilute aqueous solution at 25° showed, however, that the desired reaction occurs only at a pH greater than 11, that is, at an alkalinity greater than that likely to obtain in a cell. Moreover, when *o*-aminobenzaldehyde reacts with methyl *n*-amyl ketone at pH 13, condensation occurs not at the methyl group, but at the methylene group adjacent to carbonyl, the product being exclusively 2-methyl-3-*n*-butylquinoline (XXVI), and not the alkaloid 2-*n*-amylquinoline.



This superior reactivity of the methylene group of methyl *n*-amyl ketone indicates that such ketones cannot be the biogenetic precursors of

the alkaloids. However, when the methyl ketones are replaced by the corresponding β -keto acids which are probably also normal plant constituents, condensation proceeds readily in the pH range 5–11 and is



accompanied by decarboxylation; acetoacetic acid thus gives quinaldine, and caproylacetic acid gives 2-*n*-amylquinoline* and not the isomer (XXVI). 2-Phenylquinoline is similarly produced from benzoylacetic acid. The dependence of yield on pH is shown in Table 4.

TABLE 4

INTERACTION OF *o*-AMINOBENZALDEHYDE AND β -KETO ACIDS IN AQUEOUS SOLUTION (All reactions were conducted at 25°. Unless otherwise noted, the concentration of aldehyde was *M*/200.)

β -Keto acid	Duration, days	Percentage yield at pH						
		3	5	7	8	9	11	13 ^a
Acetoacetic <i>M</i> /125	8	Trace	8	19		66	43	0
Caproylacetic <i>M</i> /80	10			70	75	70		0 ^b
Benzoylacetic <i>M</i> /100	6		15 ^c	80		95		0 ^d

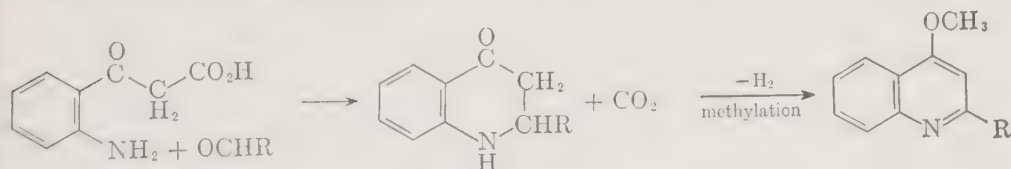
* At pH 13 high yields of the 2-alkylquinoline-3-carboxylic acids are obtained.

^b Both reactants *M*/85.

^c Both reactants *M*/300.

^d Aldehyde *M*/140, keto acid *M*/70.

Subsequently, Schöpf and Thierfelder (53) proposed an alternative scheme, as yet experimentally unrealized, whereby 4-methoxyquinoline



alkaloids are formed by the condensation of *o*-aminobenzoylacetic acid with an aldehyde, followed by dehydrogenation and methylation of the product.

* Schöpf and Lehmann (50) give m.p. 110–111° for the picrate of this substance and state that the synthetic material, m.p. 125–127°, of Späth and Piki (48) was contaminated with quinaldine picrate. The latter authors, however, give the same m.p. 125–127° not only for the picrate of the naturally occurring amylquinoline, but also for that of the base obtained by degradation of crystalline 4-hydroxy-2-*n*-amylquinoline, which could hardly contain quinaldine as impurity.

5. TABLE OF PHYSICAL CONSTANTS

TABLE 5

Compound	M.p. or b.p., °C.	Appearance	References
2- <i>n</i> -Amylquinoline	145-160/13 mm.	Colorless liquid	48, 49
Picrate	125-126		48, 49
Cuspareine	54, 56	Long needles (ligroin)	38, 39, 40
Methiodide (+H ₂ O)	156 (dec)	Yellowish leaflets (H ₂ O)	40
Methochloroplatinate (+H ₂ O)	150 (dec)		40
<i>dl</i> -Cuspareine	32-35		55
<i>dl</i> -Noreuspareine	54-55	Crystals (C ₂ H ₅ OH aq.)	55
Hydrochloride	233-234	Colorless crystals (CHCl ₃ and C ₂ H ₅ OH)	55
Picrate	148	Yellow	55
Benzoyl-	130-131	Colorless crystals (C ₂ H ₅ OH)	55
Cusparine	92	Slender needles, feathery or stellate (ligroin)	35, 42, 37, 38, 45
	91-92	Straw-yellow needles (ligroin)	42
	110-122	Thick red or amber prisms (ligroin)	40
Aurichloride	190	Yellow-red lustrous needles (HCl aq.- C ₂ H ₅ OH)	37
Chloroplatinate (+6H ₂ O)	179	Deep yellow microscopic needles	36, 37
(+3H ₂ O)	210 (dec)	Small lustrous yellow needles (HCl aq.- C ₂ H ₅ OH)	40
Citrate	174 (s)	Long, sulfur-yellow needles	42
Dichromate		Golden-yellow rectangu- lar leaflets	38
Ethiodide	206-212	Yellow prisms	42, 37, 38
Ethochloride	156	Lemon-yellow needles	37
Ethochloroplatinate	178	Golden, stellate rhombic prisms	37
Hydriodide		Yellow crystals (AcOH)	43
Hydrobromide		Long, pale yellow needles	36
Hydrochloride (+3H ₂ O)	183-184 (a) 189-191 (b)	Long thin needles	45, 36
Malate	152 (s)	Thick prisms (H ₂ O)	42
Methiodide	186, 181 (s)	Yellow needles or prisms (C ₂ H ₅ OH)	36, 42, 43
Methochloride	190	Lemon yellow needles	37
Methoaurichloride	152-153	Reddish-brown needles	37
Methochloroplatinate	210	Golden yellow needles	37

TABLE 5 (Continued)

Compound	M.p. or b.p., °C.	Appearance	References
Nitrate (+1½H ₂ O)		Yellowish, microscopic rectangular tablets	38
Oxalate (+1½H ₂ O)	140-150	Lustrous, sulfur-yellow needles	42
	(dec) 155-158		45
<i>n</i> -Propiodide	187 (s)	Yellow prisms	42
Succinate (+4½H ₂ O)	80	Greenish yellow crystals (H ₂ O)	42
(anhydrous)	113 (s)	Almost white crystals	42
Sulfate (+7H ₂ O)		Prismatic needles	36
Tartrate (+H ₂ O)	161-162 (s)	Micr. yellow needles	42
Tri-iodide (+2H ₂ O)		Dark grey-green microscopic needles	38
Amino-	205-206	Felted needles (C ₂ H ₅ OH)	40
Azo-β-naphthol	206	Pleochroic, felted needles	40
Chloroplatinate	(dec) 248	Broad, acute-angled yellow needles	40
Dihydrochloride	(dec) 224	Needles (precipitated in C ₆ H ₆)	40
Mercurichloride	231	Reed-like, yellow needles	40
Bromo-	91	Monoclinic prisms (C ₂ H ₅ OH)	38
Aurichloride	188-190	Shining golden-yellow needles (HCl aq.-C ₂ H ₅ OH)	38
Chloroplatinate	210-212	Dull yellow crystals (HCl aq.-C ₂ H ₅ OH)	38
Hydrobromide	239-241	Pale yellow prismatic needles (C ₂ H ₅ OH)	38
Hydrochloride		Microscopic needles (H ₂ O)	38
Nitro- (+H ₂ O)	142.5-143	Woolly needles (C ₂ H ₅ OH)	40
Aurichloride	200	Micr. yellow needles	40
Chloroplatinate	204	Micr. yellow needles	40
Hydrochloride (+H ₂ O)	149 (dec)	Clusters of thick prisms (HCl aq.)	40
Methiodide	(dec) 105	Small, yellow needles (C ₂ H ₅ OH)	40
Nitrate (+H ₂ O)	168	Fine, yellow needles (HNO ₃ aq.)	40
Sulfate (+4H ₂ O)	120	Acute-angled prisms (H ₂ SO ₄ aq.)	40
Isocusparine	194	Needles (C ₂ H ₅ OH), nacreous plates (H ₂ O)	43, 37, 45

TABLE 5 (*Continued*)

Compound	M.p. or b.p., °C.	Appearance	References
Aurichloride (c)		Lustrous thick orange-red needles	43
Chloroplatinate	210	Lustrous golden needles & plates	37
Hydriodide (+H ₂ O)		Small, lustrous, sulfur-yellow needles (AcOH)	43
Hydrobromide (+10H ₂ O)		Lustrous yellow-green plates	37
(+H ₂ O)		Pale yellow leaflets (AcOH)	43
Hydrochloride (+2½H ₂ O)		Stellate needles	37
Hydrogen oxalate	(dec) 155	Lemon-yellow crystals (aq. oxalic acid)	43
Methiodide	185	Lustrous yellow needles	37
Nitro-	239	Yellow laths (AcOH aq.)	43, 42
Pyrocusparine (nor-cusparine)	255	Felted needles (C ₂ H ₅ OH)	42, 38
Chloroplatinate	(dec) > 150	Reddish-yellow lustrous needles	42
Hydrochloride	207 (s)	Stellate clusters of needles	42
Nitro-	283 (dec)	Pale yellow needles (AcOH aq.)	43
Galipine	115.5	Prisms (ether, C ₂ H ₅ OH), needles (ligroin)	35
Aurichloride	175-176	Micr. brown-red needles	36
Chloroplatinate	174-175	Micr. yellow needles	35, 36
Hydriodide	178	Yellow crystals (HI aq.)	44
Hydrobromide	169	Yellow needles (HBr aq.)	36, 44
Hydrochloride	165	Triangular prisms	36, 46
Methiodide	146	Micr. lemon-yellow needles (C ₂ H ₅ OH)	36
Picrate	194		46
Sulfate (+7H ₂ O)	50		35
Nitro-	140	Pale yellow needles (C ₂ H ₅ OH)	41
Aurichloride	192 (dec)	Clusters of golden yellow needles	41
Chloroplatinate	227	Orange prismatic needles	41
Hydriodide (+3H ₂ O)	182	Yellow needles (C ₂ H ₅ OH)	44
Hydrobromide (+2H ₂ O)	177	Yellow needles (C ₂ H ₅ OH)	44
Hydrochloride (+½H ₂ O)	179-180 (dec)	Pale yellow hair-like needles (H ₂ O)	41

TABLE 5 (Continued)

Compound	M.p. or b.p., °C.	Appearance	References
Methiodide	170 (dec)	Stellate clusters (C ₂ H ₅ OH)	44
Nitrate	180 (dec)	Pale yellow prismatic needles (H ₂ O)	41
Sulfate (+H ₂ O)	191 (dec)	Clusters of pale yellow needles (H ₂ O)	41
Isogalipine	165	Silky needles (C ₂ H ₅ OH)	44, 46, 38
Chloroplatinate (+4H ₂ O)	198-199 (dec)	Deep yellow prisms (HCl aq.)	44, 38
Hydriodide (+H ₂ O)	206	Brownish-yellow rods (HI aq.)	44
Hydrobromide (+2H ₂ O)	223	Yellowish prisms (HBr aq.)	44
Hydrochloride (+5H ₂ O)	234	Yellowish-white tablets (HCl aq.)	44
Methiodide	109 (s)	Warty aggregates of need- les (C ₂ H ₅ OH—CH ₃ I)	44
Nitro-	237	Needles (AcOH)	44
Hydriodide (+H ₂ O)	167-172	Light yellow needles (AcOH aq.)	44
Norgalipine	225	Yellow-brown cryst. powder	44
Hydrobromide (+H ₂ O)	85	Yellow prisms (HBr aq.)	44
Hydrochloride (+1½H ₂ O)	112	Yellow prisms (HCl aq.)	44
Galipoidine	233	Needles (C ₂ H ₅ OH)	39
Aurichloride (c) (+1½H ₂ O)	170 (dec)	Light yellow needles	40
Chloroplatinate (+2½H ₂ O)	(dec) 158	Thick yellow prisms (HCl aq.-C ₂ H ₅ OH)	40
Galipoline	193	Colorless crystals (H ₂ O)	47
4-Hydroxy-2- <i>n</i> -amylquino- line	144	Crystals (H ₂ O)	48
4-Methoxy-2- <i>n</i> -amylquino- line	190-200/14 mm	Colorless liquid	48
Chloroplatinate	220 (dec)	Yellow crystals	48
Picrate	132	Yellow needles (CH ₃ OH)	48
1-Methyl-2- <i>n</i> -amyl-4- quinolone	101	Crystals (C ₂ H ₅ OH-H ₂ O)	48
1-Methyl-2-quinolone	74		49
Picrate	129-130		49

(a) Rapid heating. (b) Slow heating. (c) Abnormal composition, B₂H₇HAuCl₄. (s) Sinters below the melting point.

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CHAPTER 18

The Quinazoline Alkaloids

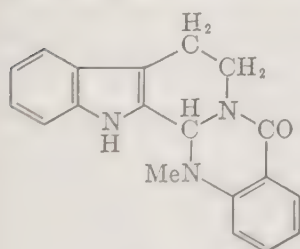
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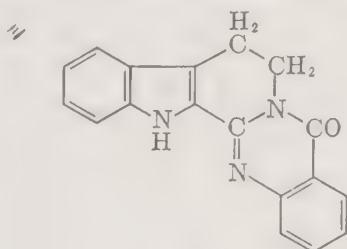
	<i>Page</i>
I. Introduction	101
II. Vasicine (Peganine).	102
1. Occurrence and Isolation	102
2. Physical and Chemical Properties	103
3. Determination of Structure	104
a. Identity of Peganine with Vasicine.	104
b. Functional Groups.	105
c. Ring Structure	105
d. Position of Hydroxyl Group; Synthesis of Vasicine.	109
4. Biogenesis of Vasicine.	110
5. Table of Physical Constants.	111
III. Alkaloids of <i>Dichroa febrifuga</i> , Lour.	112
1. Occurrence and Isolation	112
2. Physical, Chemical, and Physiological Properties.	113
3. Structural Investigations	115
4. Table of Physical Constants.	117
IV. References.	117

I. Introduction

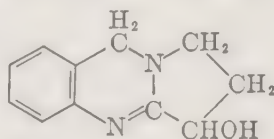
At the present time, only five alkaloids of established constitution are known to contain the quinazoline ring-system. Two of these, evodiamine (I) and rutaecarpine (II), also contain an indole nucleus and are considered along with other members of the indole group (see Chapter XIII). A third alkaloid, vasicine or peganine (III), is discussed in the present chapter. In addition, an account is given of two isomeric, interconvertible alkaloids, febrifugine and isofebrifugine, obtained from the Chinese antimalarial drug Ch'ang Shan (*Dichroa febrifuga* Lour.).



I
Evodiamine



II
Rutaecarpine
101



III
Vasicine

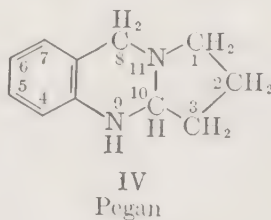
The structures of these alkaloids have recently been fully elucidated; they have been shown to be 3-substituted quinazolones.

II. Vasicine (Peganine)

I. OCCURRENCE AND ISOLATION

The alkaloid vasicine was first isolated by D. Hooper (1) in 1888 from the leaves of the Indian plant *Adhatoda vasica* Nees. (Acanthaceae), locally known as "arusa" or "bakas" and used for the treatment of asthma. Hooper stated that the alkaloid occurred in the leaves as a salt with "adhatodic acid," but neither substance was further characterized. Its chemical investigation was not commenced until 1924, when it was again isolated by J. N. Sen and T. P. Ghose (2).

Vasicine also occurs in the seeds of *Peganum harmala* L. (Zygophyllaceae), and was first isolated from this source in the laboratories of E. Merck (Darmstadt), where it was obtained from the mother liquors remaining from the technical preparation of the principal harmala alkaloids. The material from this source, which was named "peganine," was investigated by E. Späth and his school (1929-1938) (35), and its identity with vasicine soon became apparent (6, 7). In accordance with custom, the name "peganine" should therefore be abandoned in favor of the older name; recognition of the occurrence of the alkaloid in *Peganum harmala* is made, however, in the retention of the convenient systematic nomenclature introduced by Späth (16), which is based on the name "pegan" for the parent tricyclic system (IV).



Although Hooper (1) described his vasicine sulfate as feebly dextro-rotatory, the specimens of the alkaloid obtained by Sen and Ghose (2) and by E. Späth and E. Nikawitz (6) were optically inactive. After the structure (III) had been established, Späth, F. Kuffner, and N. Platzer (18) resolved the racemic base, and showed that the resulting active bases are quite readily racemized. It therefore seemed probable that racemization had occurred during the isolation of the alkaloid, and in confirmation of this theory Späth and F. Keszler (28) obtained *l*-vasicine from *Adhatoda vasica* by working under mild conditions. The same active base had been obtained independently some years earlier by A. D. Rosenfeld and D. G. Kolesnikow (30) from the flowers and stems of *Peganum harmala*. More recently, E. S. Pallares (36) has found

l-vasicine as a component of the red pigment of "Dragon's Blood" bark, in which it occurs as an ester with α,β -diphenyl- α,β -di-*n*-propylfulgenic acid.

Sen and Ghose (2) obtained a yield of only 0.2–0.4% of rather crude alkaloid from *Adhatoda vasica* leaves, but their extraction process appeared to be at fault, since Späth and Kesztlér (28) isolated over 2% of the alkaloid, nearly half of this being pure *l*-vasicine.

The air-dried leaves of *Adhatoda vasica* (530 g.) are allowed to stand with alcohol (7 l.) for two days at 15–20°. The extract is concentrated to 100 ml. in a vacuum, 1% aqueous acetic acid (200 ml.) is added and the solution again concentrated to 100 ml. The solution is filtered and extracted with ether to remove nonbasic materials; it is then basified with ammonia and extracted with ether ("extract I"). The recovered alcohol is used to make a second extraction of the leaves, which is worked up after one week ("extract II"). A third extraction is made similarly ("extract III") and finally the leaves are extracted with hot methanol in a Soxhlet apparatus for several days ("extract IV").

The crystalline material (2.14 g.) that separates from "extract I" on standing and concentration is treated with cold chloroform (100 ml.) when the vasicine dissolves leaving a small residue. The solution is concentrated in a vacuum to 20 ml., diluted with ether and extracted with 2% acetic acid.

The vasicine is recovered by basification and extraction with ether and purified by crystallization from ether-chloroform. Extracts II and III are worked up similarly, and in all 4.57 g. of pure *l*-vasicine is obtained. In addition, extract IV gives 6.97 g. of partially racemized material, so that the total yield of alkaloid is 2.18% of the dry leaves (28).

2. PHYSICAL AND CHEMICAL PROPERTIES

Vasicine forms colorless crystals sparingly soluble in water, ether, benzene, acetone (2, 6, 12, 24) and alcohol (4) and readily soluble in chloroform (2); its solutions are colorless and nonfluorescent. The ultraviolet absorption spectrum shows a maximum at 2900 Å. ($\log E = 3.8$), and rising absorption at 2200 Å. (30). The specific rotation of *l*-vasicine is strongly dependent on the nature of the solvent and the concentration of the solution (see Table 1) (17, 28). Its salts are dextro-rotatory (1, 18, 28). *dl*-Vasicine is readily resolved through the *d*-tartrate, the *l*-vasicine salt being the more sparingly soluble in methanol (18). Partial racemization occurs when the active base is sublimed in a vacuum at 170–180°, or heated with 5% hydrochloric acid for a long period. On heating, *l*-vasicine sinters strongly at 197–200°, but finally melts at 211–212°, the melting point of *dl*-vasicine, and it is probable that racemization occurs prior to melting (18).

Although it contains two nitrogen atoms, vasicine is a monoacidic base; numerous salts have been described (see Section 5). It forms precipitates with phosphotungstic, phosphomolybdic, picric and picro-ionic acids, platinic, auric and mercuric chlorides, potassium mercuric

TABLE 1
 SPECIFIC ROTATION OF *l*-VASICINE AND ITS SALTS

Substance	Solvent	Concen- tration	Temp., °C.	$[\alpha]_D$	Ref.
<i>l</i> -Vasicine (from <i>A. vasica</i>)	CHCl ₃ (Alcohol free)	2.44	14	−254°	28
	CHCl ₃ (Alcohol free)	0.56	15	−210.7°	28
	CHCl ₃ + 1 % C ₂ H ₅ OH	2.355	16	−214°	28
	CHCl ₃ + 3 % C ₂ H ₅ OH	2.52	9	−152.4°	28
	"Anesthetic Chloro- form"		16	−208°	28
	Absolute C ₂ H ₅ OH	0.455	16	−61.5°	28
<i>l</i> -Vasicine (by resolu- tion)	"Anesthetic Chloro- form"	2.66	21	−203°	18
	"Anesthetic Chloro- form"	2.01	24	−189°	18
	"Anesthetic Chloro- form"	1.04	24	−159°	18
<i>l</i> -Vasicine (from <i>P. harmala</i>)	Chloroform	1.74	24	−211°	30
<i>l</i> -Vasicine sulfate	Water	2.565	19	+19.5°	28
<i>l</i> -Vasicine	Dilute HCl	1.94	25	+31.4°	18

iodide, and potassium tri-iodide (2). It gives no color with concentrated sulfuric, nitric, or hydrochloric acid (2); addition of a drop of nitric acid to a solution of the base in concentrated sulfuric acid gives a yellow color, discharged on dilution (4). No color is given with Buckingham's (sulfuric acid-ammonium molybdate) or Marquis's reagent (sulfuric acid-formaldehyde) (2).

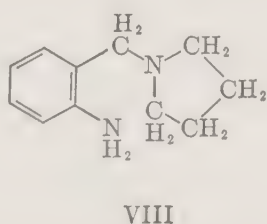
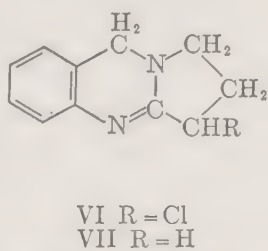
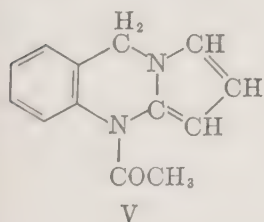
3. DETERMINATION OF STRUCTURE (35)

a. Identity of Peganine with Vasicine. In their first communication on peganine, Späth and Nikawitz (6) remarked on the possible identity of this base with vasicine, since the two alkaloids are isomeric, have similar melting points, and form hydrochlorides and chlorodesoxy derivatives of the same melting point. Moreover, oxidation experiments (see below) indicate that both bases are quinazoline derivatives. The identity of the two alkaloids was established by Späth and Kuffner by a direct comparison of peganine, first (7) with a sample of vasicine prepared by Merck, and later (15) with a sample obtained from the Indian workers. Minor differences in the described properties of vasicine from those of peganine were subsequently proved (12) to be due to errors in the former (2, 5, 24).

b. Functional Groups. Vasicine has the molecular formula $C_{11}H_{12}ON_2$. It is a monoacidic, tertiary base, forming a monomethiodide (34), $C_{12}H_{15}ON_2I$. The derived hydroxide is stable at 100° , and its properties as described by Sen and Ghose (2) suggest that it is not the quaternary hydroxide but the related carbinol-base.

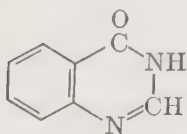
Vasicine readily decolorizes aqueous potassium permanganate or bromine water (5) but it is resistant to catalytic hydrogenation (5, 6, 12). It contains neither a methoxyl group (2, 6) nor a methylimino group (5, 6) and it is devoid of phenolic (12, 24) and ketonic (6) properties. Vasicine contains one active hydrogen atom (Zerevitinov) (6), and when treated with hot acetic anhydride it gives a monoacetyl derivative, which from its ready hydrolysis must be an *O*-acetyl rather than a *N*-acetyl compound (6, 17). [More vigorous treatment with acetic anhydride and sodium acetate (5) gives a compound, $C_{13}H_{12}ON_2$, later shown (17) to be *N*-acetylpegadiene (V).] The presence of an alcoholic hydroxyl group is supported by the conversion of the alkaloid by phosphoryl chloride into chlorodesoxyvasicine $C_{11}H_{11}N_2Cl$ (VI) (3, 6), which on reduction with zinc and acid gives desoxyvasicine, $C_{11}H_{12}N_2$ (peg-9-en, VII) (3, 15). This base is also resistant to catalytic hydrogenation (12).

Reduction of vasicine with sodium and amyl alcohol produces a base, dihydrodesoxyvasicine, $C_{11}H_{14}N_2$ ("desoxytetrahydropeganine," pegan, IV) (6, 12) which contains one active hydrogen atom and forms a monoacetyl derivative, and hence possesses an imino group. Reduction must therefore have occurred at a $:C=N$ linkage. A small amount of dihydrovasicine (pegan-3-ol) is also formed in this reduction (17). Further reduction with tin and hydrochloric acid affords "desoxyhexahydropeganine" [subsequently shown (17) to be *N*-*o*-aminobenzylpyrrolidine (VIII)].

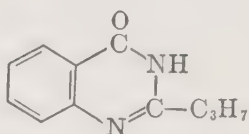


c. Ring Structure. The first indication of the presence of a quinazoline ring system was obtained by T. P. Ghose (3, 5) who identified 4-quinazolone (IX) as a product of the oxidation of vasicine with acid permanganate. The presence of such a structure is supported by the production of anthranilic acid by potash fusion of vasicine, and Ghose proposed the structure X for the alkaloid. This was soon disproved by A. K. De and J. N. Rây (4), who synthesized 2-*n*-propyl- and 2-*iso*-propyl-4-quinazolone, neither of which was identical with vasicine.

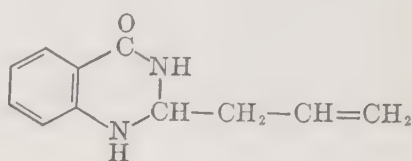
Subsequently, the Indian chemists jointly proposed the structure (XI) (5).



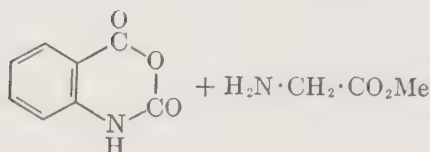
IX



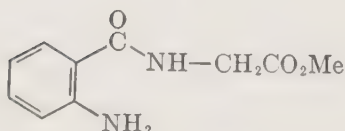
X



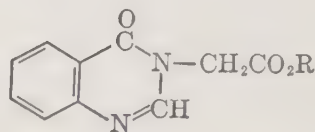
XI



Isatoic anhydride

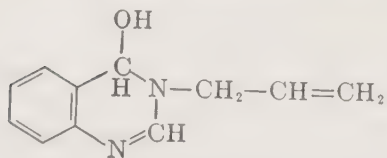


XIII

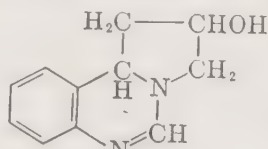


XII R = H
XIII R = Me

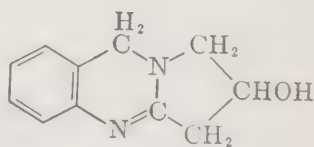
By oxidizing the alkaloid with alkaline permanganate, Späth and Nikawitz (6) obtained a different and more significant result. The product was an acid, $C_{10}H_8O_3N_2$, which was degraded by alkaline hydrolysis to anthranilic acid and glycine, and by decarboxylation to 3-methyl-4-quinazolinone. The structure of the acid is therefore XII, confirmation being obtained by the synthesis of its methyl ester (XIII) (8). This degradation, which clearly disproves the structure XI, led Späth and Nikawitz to propose XIV as the most likely structure for vasicine. Tricyclic structures such as XV or XVI were also considered, but were provisionally rejected on the ground that oxidation of such substances would be expected to give dicarboxylic acids (6, 8).



XIV



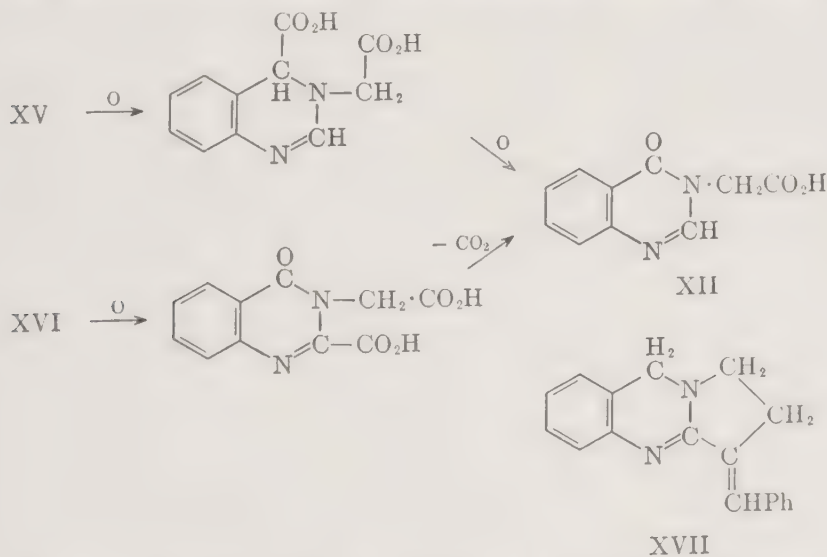
XV



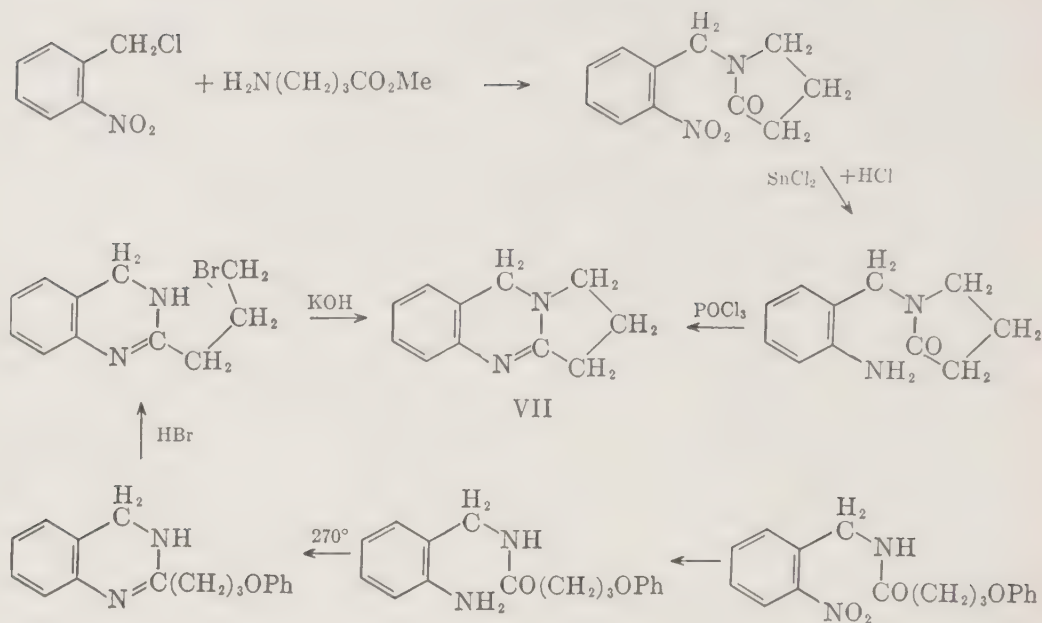
XVI

Miss T. M. Reynolds and R. Robinson (9) pointed out that structure XIV represents the carbinol base derived from a 3-allylquinazolinium salt, and would be very unlikely to form an *O*-acetyl- or a chlorodesoxy-derivative. Moreover, its salts would be quaternary and formed with loss of a molecule of water, whereas the salts of vasicine have the normal composition. Synthesis of XIV from 3-allylquinazolinium iodide and alkali confirmed that it had entirely different properties from those of

vasicine. W. E. Hanford, P. Liang, and R. Adams (12) further criticized the structure XIV on the ground that it fails to account for the resistance of vasicine and desoxyvasicine to catalytic hydrogenation. Moreover, as previously pointed out by Narang and Rây (10), desoxyvasicine is not identical with the known 3-allyl-3:4-dihydroquinazoline (13), the structure of which was confirmed by a new and unequivocal synthesis (12). 3-Allyltetrahydroquinazoline was also shown to differ from dihydrodesoxyvasicine (pegan), and both synthetic compounds were readily susceptible to catalytic hydrogenation. The alkaloid must therefore possess a tricyclic structure (12, 15). The ready loss of one carbon atom and the formation of a monocarboxylic acid in the permanganate oxidation is readily accommodated by XV and XVI. In the former case, quinazolines are known to be very susceptible to oxidation at C₄, so that the oxidative elimination of a carboxyl group from this position seems possible. In the latter case, C. Paal and F. Krecke (14) have shown that 3-phenyl-4-quinazolone-2-carboxylic acid is readily decarboxylated, and the presence of a carboxymethyl group instead of a phenyl group at position 3 may similarly facilitate decarboxylation (15, 20). The latter type of structure (XVI) was preferred by Hanford and Adams (12, 20) because desoxyvasicine resembles 2-alkylquinazolones in forming a benzylidene derivative (XVII).



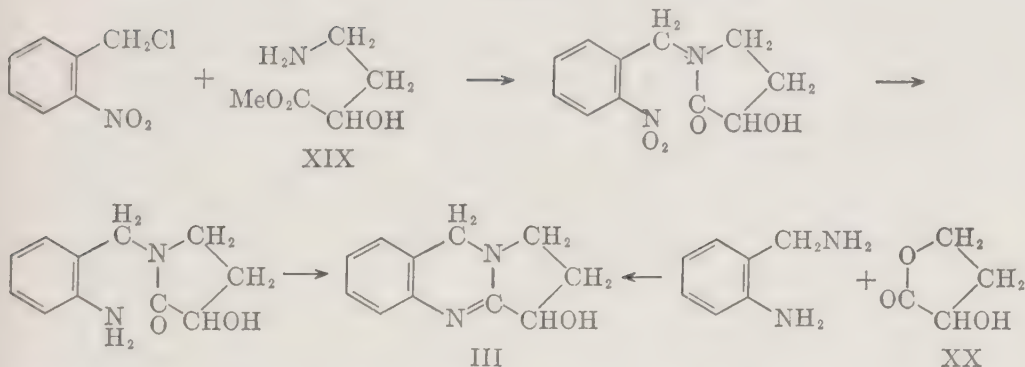
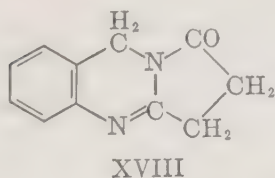
A decision between the two types of ring structure, through the synthesis of desoxyvasicine (peg-9-en, VII), was reached independently by E. Späth, F. Kuffner, and N. Platzer (15) and by W. Hanford and R. Adams (20). In the first case (15) *o*-nitrobenzyl chloride reacted with methyl γ -aminobutyrate to give *N*-*o*-nitrobenzylpyrrolidone, which by reduction to the amine and cyclization with phosphoryl chloride afforded the desired product (VII). Its identity with desoxyvasicine was further confirmed by reduction to dihydrodesoxyvasicine (pegan, IV).



Hanford and Adams (20) reduced the *o*-nitrobenzylamide of γ -phenoxybutyric acid, and cyclized the product at 270° . Hydrobromic acid removed the phenoxy group and the resulting 2- γ -bromopropyl-3:4-dihydroquinazoline cyclized to VII on addition of alkali.

Evidence for the presence of the ring-structure VII in vasicine was also adduced by H. R. Juneja, K. S. Narang, and J. N. Rây (22, 23). Peg-9-en-1-one (XVIII), synthesized from *N*-*o*-nitrobenzylsuccinimide by reductive cyclization with stannous chloride (25), gave on electrolytic reduction a product identical with that obtained by similar reduction of vasicine, and considered to be pegan (IV). This work was subsequently questioned by Späth and N. Platzer (29) and by Späth, F. Kuffner, and J. Lintner (31) in whose hands the electrolytic reduction of both vasicine and XVIII gave rise to *o*-aminobenzylpyrrolidine (VIII) and therefore failed to afford the desired proof of the ring-structure of the alkaloid. After further investigation, however, the Indian chemists (33) upheld their original claim, but agreed that on prolonged reduction the product (IV) was further reduced to VIII. The discrepancy between the results of the two schools may be due, at least in part, to the known susceptibility of the course of electrolytic reduction processes to minor variations in conditions and especially to the presence of impurities in the electrode material.

d. Position of Hydroxyl Group; Synthesis of Vasicine. To complete the elucidation of the structure of vasicine it remained only to decide the position of the hydroxyl group, and this was quickly achieved by Späth, Kuffner, and Platzer (16) by the synthesis of the alkaloid. γ -Butyrolactone was converted into γ -phthalimido- α -hydroxybutyric acid by an



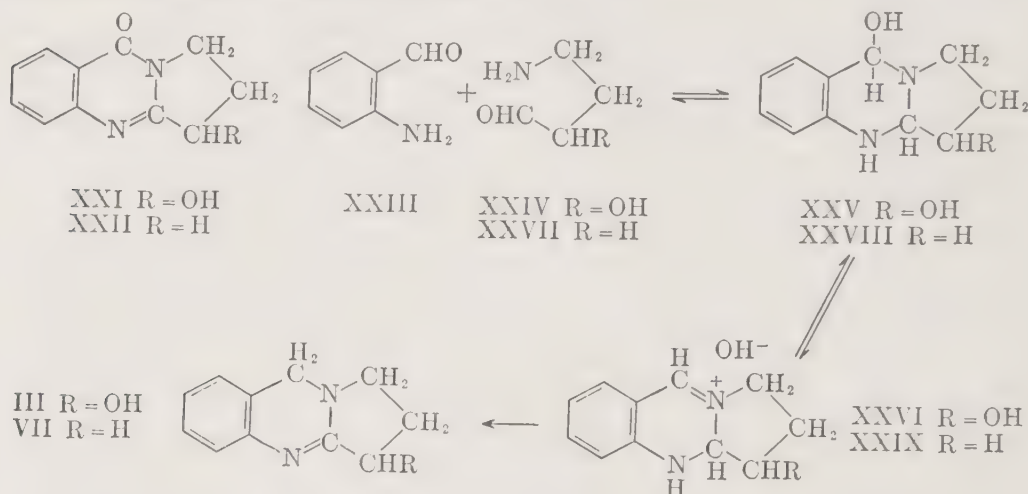
improvement of the method of E. Fischer and A. Göddertz (37) and thence into methyl γ -amino- α -hydroxybutyrate (XIX). This substance was treated with *o*-nitrobenzyl chloride and the derived product reduced with stannous chloride; on distillation of the resulting 3-hydroxy-1-*o*-aminobenzylpyrrolidone cyclization to vasicine (III) occurred.

Späth and Platzner (27) subsequently described a simpler synthesis of the alkaloid, by condensing *o*-aminobenzylamine with α -hydroxybutyrolactone (XX); with butyrolactone itself, peg-9-en (desoxyvasicine) (VII) was obtained.

A mixture of *o*-aminobenzylamine (0.68 g.) and α -hydroxybutyrolactone (0.59 g.) is heated under nitrogen for 20 min. in a metal bath at 200°. The water formed is removed by reducing the pressure, and the mixture is again heated at 200° for 20 min. and, after removal of the water, for a further 15 min. Distillation of the crude product in a high vacuum from a bath at 180–210° gives a resin which is boiled with water. The vasicine dissolves, leaving an insoluble tar. After the addition of 11.2 cc. of 1*N* hydrochloric acid the aqueous layer is extracted with ether to remove non-basic material, saturated with salt and basified with ammonia. The vasicine is recovered by ether extraction and the whole purification process is repeated using a smaller volume of water. Finally the base is purified by sublimation at 170–190° (0.03 mm.) and by crystallization from methanol and ether; m.p. 211–212° (evacuated tube), yield 0.216 g.

Independent evidence for the position of the hydroxyl group in vasicine was obtained by Morris, Hanford, and Adams (21). The oxidation of the alkaloid by hydrogen peroxide, previously observed by Ghose, Krishna, Narang, and Rây (5, 32), was shown to give rise to the corresponding quinazolone (XXI). A similar oxidation of desoxyvasicine (VII) produced peg-9-en-8-one (XXII), which in agreement with the assigned structure formed a benzylidene derivative. Its structure was also confirmed by synthesis (21, 19). Treatment of XXII with lead

tetraacetate caused the introduction of an acetoxy group, and after mild hydrolysis the product was identical with the oxidation product (XXI) obtained from vasicine. Since C₃ is the only point in XXII likely to be attacked by lead tetraacetate, this must be the position at which the hydroxyl group in vasicine is located.



4. BIOGENESIS OF VASICINE

C. Schöpf and F. Oechler (26) have discussed possible methods by which vasicine might be elaborated by the plant, and consider that the most probable progenitors are *o*-aminobenzaldehyde (XXIII) and γ -amino- α -hydroxybutyraldehyde (XXIV), condensation of which should lead to the pseudo base (XXV) and thence to the quaternary base (XXVI). Conversion of the latter into vasicine (III) requires the transference of two hydrogen atoms from N₁—C₂ to N₃—C₄, under the influence of a suitable catalyst (enzyme). The aldehyde XXIV is unknown, but the feasibility of this scheme was confirmed by the successful synthesis of desoxyvasicine (VII) from XXIII and γ -aminobutyraldehyde (XXVII) (liberated *in situ* from its acetal). These substances react in dilute aqueous solution at pH 5, giving a yellow solution from which, after four days at 30°, picric acid precipitates the picrate of (XXIX) in 75–78% yield. When the same solution is shaken with palladium and hydrogen, part of the product undergoes the desired hydrogen transference and an 18% yield of desoxyvasicine (VII) is obtained. The principal product, however, is *o*-aminobenzyl alcohol, which is produced in 79% yield. The formation of this reduction product of *o*-aminobenzaldehyde in such large amount can be explained by assuming that the initial condensation is reversible, and that the equilibrium is altered in favor of the original reactants by the removal of the aldehyde by reduction at a rate greater than that of the hydrogen-transference reaction.

5. TABLE OF PHYSICAL CONSTANTS

TABLE 2

Compound	M.p. or b.p. °C.	Appearance	References
Vasicine (peg-9-en-3-ol)	211-212 <i>v</i>	Colorless needles (square prismatic)	1, 2, 7
Aurichloride		Rosettes of orange-brown platelets	2
Chloroplatinate		Yellow-brown needles	2
Hydriodide	195	Colorless needles (MeOH)	2, 34
Hydrochloride	205-207 <i>v</i>	Colorless needles (EtOH-Et ₂ O)	2, 5, 7
Methiodide	190	Needles (MeOH)	2, 5, 34
Methohydroxide	100	Pale brown prisms (C ₆ H ₆ -ligroin)	2
Picrate	190-191 (dec)	Silky, felted needles (MeOH)	26, 2
Picolonate	177-179 (dec) <i>v</i>		31
Sulfate (+2H ₂ O)		Needles (H ₂ O)	2
Acetyl-	122-123 <i>v</i>	Crystals (C ₆ H ₆ -ligroin)	17
<i>N</i> - <i>o</i> -Aminobenzylpyrrolidine ("des-oxyhexahydropeganine")	31-32	Crystals (from liquid state)	17, 6
Dipicolonate	213-215 <i>v</i>		31
3-Chloropeg-9-en (chlorodesoxyvasicine)	136-137 <i>v</i>	Lustrous leaflets (Et ₂ O or C ₆ H ₆ -C ₆ H ₁₄)	3, 6, 7
3-Chloropeg-9-en-8-one	109	White needles (ligroin)	21
Pega-1:3-diene	210-211 <i>v</i>		17
Acetyl-	163-164.5 <i>v</i>		17, 5
Pegan (dihydrodesoxyvasicine, "des-oxytetrahydropeganine")	74 <i>v</i>	Crystals (Et ₂ O-ligroin)	6, 31
Picrate	185	Crystals (EtOH)	12
Picolonate	191-193 <i>v</i>		31, 33
Acetyl-	190-200/0.1 mm.	Yellow oil	6
Pegan-3-ol (dihydrovasicine)	132-133 <i>v</i>	Crystals (Et ₂ O or H ₂ O)	17
Picolonate	188-190 (dec) <i>v</i>		31, 33
Pegan-1-one	115		33
Peg-2-en	92		33
Picolonate	224-228 (dec)	Needles (EtOH)	33
Peg-9-en (desoxyvasicine) (+2H ₂ O)	77	Prismatic needles (H ₂ O)	3
(+½H ₂ O)	87-88	(By drying over H ₂ SO ₄)	3
(anhydr.)	101-102 <i>v</i>		15, 20, 27
Chloroplatinate		Orange-yellow	3
Hydrochloride	255-256	Prismatic needles (EtOH-Et ₂ O)	3
Oxalate	235	Crystals (EtOH-Et ₂ O)	12
Picrate	205-206	Crystals (EtOH)	12
Picolonate	236-237 (dec) <i>v</i>	Crystals (EtOH)	31
Benzylidene-	161-163	Yellow needles (EtOAc)	20
Peg-9-en-3-ol-8-one	213-214	Microcryst. (H ₂ O)	5, 21, 32
Peg-9-en-1-one	191 <i>v</i>	Crystals (H ₂ O or sublimation)	29
Peg-9-en-8-one	110-111 <i>v</i>	Colorless needles (ligroin)	19, 21
Benzylidene-	137-139	Yellow crystals (ligroin)	21
4(3)-Quinazalone-3-acetic acid	235-237 <i>v</i>	Small, thick needles (subl.)	6
Methyl ester	152.5 <i>v</i>	Colorless crystals (acetone-Et ₂ O)	6
Methylamide	233-235 <i>v</i>	Lustrous, felted needles (subl.)	6

v; in evacuated tube

III. Alkaloids of *Dichroa febrifuga*, Lour.

1. OCCURRENCE AND ISOLATION

Reports (38, 39, 40, 41) of the antimalarial activity of the Chinese drug Ch'ang Shan, the powdered root of *Dichroa febrifuga* (Saxifragaceae), have led to its chemical investigation concurrently by several groups of workers. Although earlier investigations (39, 40) failed to reveal the presence of alkaloids, C. S. Jang and coworkers (41) showed the pharmacological activity of the drug to be due to its alkaloid content, and they isolated two bases, "Dichroine A" and "Dichroine B," as their hydrochlorides, the latter showing powerful antimalarial activity. Later, however (42), they found that these preparations were somewhat impure. In the meantime, J. B. Koepfli, J. F. Mead, and J. A. Brockman, Jr. (43, 44), isolated two pure isomeric, crystalline alkaloids, $C_{16}H_{19}O_3N_3$, which they named febrifugine and isofebrifugine. The separation and characterization of these bases was complicated by their ready interconvertibility on heating, and by the dimorphism (44) of febrifugine. T. Q. Chou, F. Y. Fu, and Y. S. Kao (45), working with Jang's material (42), described the isolation of *three* isomeric, interconvertible crystalline alkaloids, " α -, β -, and γ -dichroines," together with umbelliferone, 4-quinazolone and an alkaloid "dichroidine" (42), $C_{18}H_{23}O_3N_3$. " α -Dichroine" appears to be identical with isofebrifugine, while β - and γ -"*dichroines*" probably correspond to the two crystalline forms of febrifugine (44). Finally, F. A. Kuehl, Jr., C. F. Spencer and K. Folkers (46) independently obtained two crystalline alkaloids agreeing in properties with febrifugine and isofebrifugine.

The total alkaloid content of the Chinese root is 0.1–0.15% (43, 46), but that of Indian root is only about one tenth as great (46). The leaves of *D. febrifuga* also contain febrifugine (43, 44, 46), but in much smaller amount than the roots; nevertheless, the leaves (known as "Shuu Chi," or in Yunnan as "Chunine") have a high antimalarial activity and probably contain some other active alkaloid (44). Febrifugine has also been isolated from hydrangea leaves (51).

According to Koepfli, Mead, and Brockman (44) the alkaloids are best isolated by extracting the ground plant material with 0.1 *N* hydrochloric acid until the extract no longer gives Dragendorff's reaction, followed by adsorption from the acidic extract on to Fuller's earth (150 g./g. of alkaloids). The bases are removed from the earth by treatment with sodium carbonate and extraction with butanol. After further purification by twice extracting into acid and back into butanol-chloroform (1:4), febrifugine is crystallized as the dihydrochloride from 90% ethanol. Basification of the mother liquor gives crude isofebrifugine which is purified by crystallization from methanol. On a smaller scale, the two alkaloids are best separated by chromatog-

raphy from chloroform on alumina (44, 46), febrifugine being the more strongly adsorbed.

Kuehl, Spencer and Folkers (46) crystallized the mixed alkaloids as oxalate. The finely ground root (2467 g.) is moistened with water and extracted with methanol in a Soxhlet for 3 days. The solution is concentrated in a vacuum and the concentrate (about 800 ml.) is brought to pH 3 with dilute hydrochloric acid and extracted continuously with chloroform for 20 hours to remove impurities. It is then brought to pH 8 with sodium bicarbonate and the alkaloids are removed by extraction with chloroform for 20 hours. After evaporation of the chloroform, the brown residue (3.78 g., 0.15%) is dissolved in 50% methanol (25 ml.) and oxalic acid is added to pH 3. The resulting solution is warmed, filtered, and concentrated. The gummy residue crystallizes from methanol-acetone, the oxalate (1.453 g., 0.052%) having m.p. 199–201°, raised to 215–218° (decomp.) by recrystallization from 50% aqueous methanol; $[\alpha]_D^{25} + 17^\circ$ ($c = 1$ in water).

An aqueous solution of the oxalate (4.38 g.) is brought to pH 8 with sodium bicarbonate and extracted for 3 hours with chloroform. The residue obtained by evaporation of the extract in a vacuum is dissolved in alcohol when it deposits crystalline isofebrifugine ("Alkaloid I") (2.74 g., m.p. 131–132°). On standing, the mother liquor deposits crude crystalline febrifugine ("Alkaloid II"), m.p. 135–142°.

2. PHYSICAL, CHEMICAL AND PHYSIOLOGICAL PROPERTIES

Febrifugine and isofebrifugine are colorless, and possess practically identical ultraviolet (44, 46) and infrared (46) absorption spectra. The ultraviolet absorption of febrifugine shows maxima at 2250 Å. ($E\%$ 895), 2660 Å. ($E\%$ 246), 3010 Å. ($E\%$ 109), and 3130 Å. ($E\%$ 98), with an inflection or subsidiary maximum at 2750 Å. ($E\%$ 210 approx.). The infrared absorption showed bands at 6.03, 6.26, 6.45 and 6.78 μ .

Both alkaloids are dextrorotatory, the optical activity varying considerably with the solvent and concentration, as shown in the accompanying table.

TABLE 3
SPECIFIC ROTATIONS OF FEBRIFUGINE AND ISOFEBRIFUGINE

<i>Febrifugine</i>					<i>Isofebrifugine</i>				
Solvent	<i>c</i>	T, °C.	$[\alpha]_D$	Ref.	Solvent	<i>c</i>	T, °C.	$[\alpha]_D$	Ref.
Chloroform	0.5	25	+ 6°	44	Chloroform	0.35	25	+131°	44
Ethanol	0.5	25	+28°	44	Chloroform	0.8	25	+120°	46
Ethanol	1.4	17	+21°	46	Ethanol	1.5	25	+ 31°	46

Febrifugine is soluble to the extent of 1–3% at room temperature in water, ethanol, acetone, or chloroform. It is very soluble in methanol-chloroform and water-ethanol mixtures, and very insoluble in ether,

benzene, and light petroleum. It is easily extracted from alkaline solution by butanol (distribution coefficient, $K = 31$) and by 1:4 butanol-chloroform mixture ($K = 11$), but not well by chloroform alone ($K = 0.7$). Isofebrifugine is approximately 0.5% soluble in water, 3–4% soluble in methanol and 7% soluble in chloroform, at room temperature. It is very soluble in methanol-chloroform mixtures, almost insoluble in acetone and very insoluble in ether, benzene, and light petroleum. It is easily extracted from basic solution by chloroform ($K = 10$) or butanol ($K = 6$) (44).

Febrifugine is dimorphous. As usually obtained, by crystallization from ethanol, it forms colorless needles of m.p. 139–140°, but a higher melting form, m.p. 154–156°, can be obtained by precipitation from a saturated solution of the hydrochloride by the addition of 2.5 N sodium hydroxide (44) or by crystallization of molten febrifugine (45) or isofebrifugine (44, 45). Both forms have the same optical rotation (44), give the same salts (44, 45), and give the same zone on chromatography (44), and either form can be obtained from a chloroform solution by appropriate seeding (44).

Both febrifugine and isofebrifugine form crystalline salts, and although they usually react as monoacidic bases, both form crystalline dihydrochlorides in alcoholic solution, that from isofebrifugine being very hygroscopic. Potentiometric titration of isofebrifugine shows the presence of two basic groups, of pK_{B_1} 5.7 and pK_{B_2} 12 respectively; pK_{B_1} for febrifugine is estimated as 6.3 from distribution coefficient measurements.

When isofebrifugine is heated for an hour or more in boiling alcoholic or aqueous solution, or at its melting point for a few minutes, it is partially converted into febrifugine (44, 45). The reverse change occurs when febrifugine is heated in chloroform solution for 3 hours, about 43% of isofebrifugine being isolable by chromatography (44).

The alkaloids readily give a precipitate with Dragendorff's reagent, a concentration of 6 p.p.m. being just detectable. Meyer's reagent, on the other hand, is a very insensitive test (44).

The antimalarial activity of febrifugine against *Plasmodium gallinaceum* in chicks has been estimated to be 16 (46) to 64 (44) times that of quinine; a dose of 4 mg./kg. is reported as curative (45). The alkaloid is a hundred times as active as quinine against *P. lophurae* in ducks, and an equal or greater activity is shown against the trophozoites of *P. cynomolgi* in monkeys (47). The toxicity is rather high; about 5 mg./kg. is toxic to chicks, and for the white mouse an LD_{50} of 2.5–3.0 mg./kg. was found. The toxic effects on rhesus monkeys have also been studied (47). Clinical trials were discouraging (48). Isofebrifugine possesses very little antimalarial activity (44).

3. STRUCTURAL INVESTIGATIONS

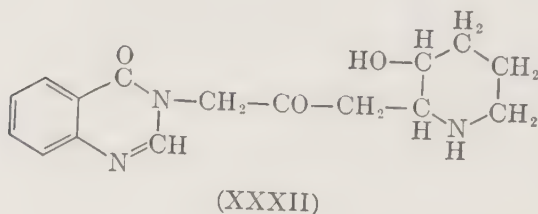
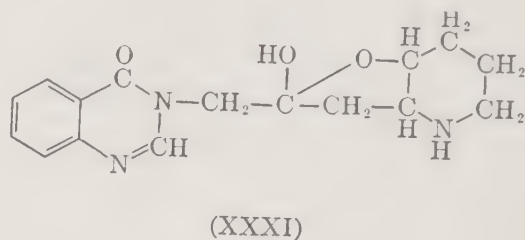
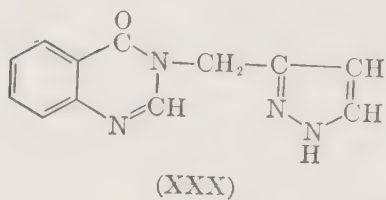
The molecular formula of febrifugine and of isofebrifugine seems to be firmly established as $C_{16}H_{19}O_3N_3$ (43, 46), although Chu, Fu, and Kao (45) ascribe to their "dichroines" the formula $C_{16}H_{21}O_3N_3$. Neither alkaloid contains a carboxyl, methoxyl or methylenedioxy group, while *N*-methyl groups also appear to be absent (44, 45). Both alkaloids reduce Tollens's reagent, but neither aldehyde nor methyl ketone groups can be detected. Febrifugine contains a carbonyl function, however, as it gives an oxime and a semicarbazone; corresponding derivatives have not been obtained from isofebrifugine (44). Both alkaloids form basic *N*-nitroso derivatives, indicating the presence of one imino group (44, 45), and both form nonbasic dibenzenesulfonyl derivatives (44); they are also stated to form amorphous tribenzoyl derivatives (45).

On hydrogenation in ethanolic solution at room temperature, both alkaloids absorb one mole of hydrogen. In each case, a crystalline dihydro derivative can be isolated, but a portion of the product remains amorphous, suggesting that the reduction produces more than one stereoisomer. Dihydrofebrifugine forms no carbonyl derivatives, and neither dihydro alkaloid reduces Tollens's reagent. Hydrogenation causes practically no change in the ultraviolet absorption spectrum (44).

Both alkaloids are readily oxidized by periodate to give the same optically inactive crystalline product, of probable formula $C_{16}H_{17}O_3N_3$ (44). With alkaline permanganate, both alkaloids yield 4-quinazolone (IX) (44, 45), and on alkaline hydrolysis they give anthranilic acid, formic acid and a little ammonia, together with an oily base, the vapors from the pyrolysis of which give a red pine-shaving reaction (44, 45). Hydrolysis of dihydrofebrifugine also gives anthranilic acid and formic acid, together with a base which gives a crystalline benzenesulfonyl derivative of tentative formula $C_8H_{13}ON_2(C_6H_5SO_2)_3$ (44).

The presence of a quinazolone structure in these alkaloids, already indicated by the results of their degradation, is strongly supported by the very close correspondence of their ultraviolet absorption spectra to those of known quinazolones, and particularly of 3-allyl-4-quinazolone. Their ease of hydrolysis is also typical of a 3-substituted 4-quinazolone, and the isolation of a C_8 fragment containing two nitrogen atoms from the hydrolysis of dihydrofebrifugine is in agreement with the presence of such a structure, and further suggests that the 4-quinazolone system is substituted only at the 3-position (44). Interaction of the periodate oxidation product of the alkaloids with semicarbazide gives rise to 3-(3-pyrazolylmethyl)-4-quinazolone (XXX), and this observation led Koepfli, Brockman, and Moffat (50) to suggest that the alkaloids are the

two diastereoisomeric hemiketals (XXXI) derived from the keto alcohol (XXXII). This view has been supported by further investigation and confirmed by synthesis (51).



Febrifugine is the first alkaloid to be isolated from a member of the Saxifragaceae, and it is the first known alkaloid outside the cinchona group to possess marked antimalarial activity. Its quinazoline structure is of particular interest in view of the recorded antimalarial activity of some synthetic quinazolines (49). A number of synthetic analogues of XXXII have been prepared and tested as antimalarials (51).

4. TABLE OF PHYSICAL CONSTANTS

TABLE 4

Compound	M.p., °C.	Crystal form	References
Dichroidine (C ₁₈ H ₂₃ O ₃ N ₃)	212–213	Small prisms (acetone)	45
Febrifugine	139–140*	Colorless needles (EtOH)	43
(“Alkaloid II”)	140–142	Colorless needles (EtOH)	46
(“β-Dichroine”)	145	Colorless needles (CHCl ₃)	45
Dimorphous form	154–156*		44
(“γ-Dichroine”)	160	Silky needles (acetone)	45
Hydrochloride (B·HCl)	220	Prisms (EtOH)	45
Dihydrochloride (B·2HCl)	220–222*		43, 44
(dec)			
(of “β-dichroine”)	236	Needles (EtOH)	45
Sulfate (B ₂ ·H ₂ SO ₄)	224	Needles (EtOH)	45
Dibzenzenesulfonyl-	148–148.5*	Crystals (EtOH-H ₂ O)	44
Dihydro-	192–193*	Colorless crystals (EtOH)	44
Nitroso-	171.5–172.5*	Rhombic prisms (EtOH)	44, 45
Oxime	224–225*	Crystals (EtOH-H ₂ O)	44
	(dec)		
Semicarbazone	187–188*	Crystals (EtOH)	44
	(dec)		
Isofebrifugine	129–130*	Thick prisms (MeOH)	43, 44
(“Alkaloid I”)	131–132	Colorless needles (EtOH)	46
(“α-Dichroine”)	136	Colorless prisms (EtOH)	45
Hydrochloride (B·HCl)	210	Prismatic needles (EtOH)	45
Dihydrochloride		Hygroscopic	43
Oxalate (B ₂ ·C ₂ H ₂ O ₄)	212–213	Colorless crystals	46
	(dec)	(MeOH-H ₂ O)	
Sulfate (B ₂ ·H ₂ SO ₄)	220	Silky needles (EtOH)	45
Dibzenzenesulfonyl-	182.5–183.5*	Crystals (EtOH-H ₂ O)	44
Dihydro-	156.5–157.5*	Crystals (acetone)	44
Nitroso-	185–186.5*	Needles (EtOH)	44, 45

* Corrected m.p.

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CHAPTER 19

Lupin Alkaloids

NELSON J. LEONARD

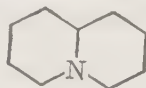
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	<i>Page</i>
I. Occurrence and Constitution	120
II. Extraction Procedure	128
III. Structure of the Alkaloids	130
1. Lupinine, $C_{10}H_{19}NO$	130
a. The Structure of Lupinine	131
b. Synthesis of Norlupinane (Quinolizidine)	137
c. Synthesis of Lupinine	141
d. Isomers of Lupinine	142
2. Cytisine, $C_{11}H_{14}N_2O$	143
a. The Structure of Cytisine	144
b. Synthetic Experiments with Cytisine	155
3. Sparteine, $C_{15}H_{26}N_2$	156
a. The Structure of Sparteine	156
b. Isomers of Sparteine	162
c. Synthesis of Sparteine	163
4. Lupanine, $C_{15}H_{24}N_2O$	166
5. Anagyrine, $C_{15}H_{20}N_2O$	169
6. Alkaloids Related to Sparteine	173
a. α -Isosparteine, $C_{15}H_{26}N_2$	174
b. Aloperine, $C_{15}H_{24}N_2$	174
c. Pusilline, $C_{15}H_{28}N_2$	174
d. Retamine, $C_{15}H_{26}N_2O$	175
7. Alkaloids Related to Lupanine	175
a. α -Isolupanine, $C_{15}H_{24}N_2O$	175
b. $C_{15}H_{24}N_2O$	176
c. Hydroxylupanine, $C_{15}H_{24}N_2O_2$	176
d. $C_{15}H_{24}N_2O_2$	177
e. Trilupine, $C_{15}H_{24}N_2O_3$	177
f. Sophocarpine, $C_{15}H_{24}N_2O$	178
g. Matrine, $C_{15}H_{24}N_2O$	178
h. Oxymatrine, $C_{15}H_{24}N_2O_2$	182
i. Aphylline, $C_{15}H_{24}N_2O$	183
j. Aphyllidine, $C_{16}H_{22}N_2O$	184
k. Monspessulanine, $C_{15}H_{22}N_2O$	185
l. Pl, $C_{15}H_{22}N_2O$	185
m. Ammothamnine, $C_{15}H_{24}N_2O_3$	185
n. Sophoridine, $C_{15}H_{26}N_2O$	186
o. Virgiline, $C_{16}H_{26}N_2O_2$	186
p. Dilupine, $C_{16}H_{26}N_2O_2$	186

	<i>Page</i>
8. Alkaloids Related to Anagyrine	186
a. Sophoramine, $C_{15}H_{20}N_2O$	186
b. Thermopsine, $C_{16}H_{20}N_2O$	186
c. Homothermopsine, $C_{17}H_{24}N_2O$	187
d. Baptifoline, $C_{16}H_{20}N_2O_2$	187
e. Rhombifoline, $C_{16}H_{20}N_2O_2$	188
f. $C_{16}H_{20}N_2O_5$	188
9. Alkaloids with a Piperidine Nucleus	188
Ammodendrine, $C_{12}H_{20}N_2O$	188
10. Miscellaneous Lupin Alkaloids.	189
a. Calycotamine, $C_{11}H_{15(17)}NO_3$	189
b. <i>d</i> -Calycotomine, $C_{12}H_{17}NO_3$	189
c. <i>dl</i> -Calycotomine, $C_{12}H_{17}NO_3$	190
d. Pentalupine, $C_{16}H_{30}N_2O$	190
e. Sophochrysine, $C_{13-15}H_{21-19}N_3O_2$	190
f. P2, $C_{11}H_{18}N_2O$	190
g. P4.	190
h. Base E.	190
i. Sarothamnine, $C_{30}H_{50}N_4$	190
j. Laburnine, $C_8H_{15}NO$	190
IV. Stereochemistry of the C_{15} -Lupin Alkaloids.	191
V. References.	192

I. Occurrence and Constitution

The "lupin alkaloids" are found in a wide variety of plants and small trees, such as broom, lupin, gorse, and laburnum, which are used diversely in gardens, for fodder, and as sand-binders. The alkaloids as a group are toxic, but as individuals find some use in veterinary medicine and in insecticide preparations. Chemical similarity rather than plant distribution links these alkaloids, since most of them contain—in actual or modified form—the quinolizidine ring structure (I). This basic



I

nucleus (called variously quinolizidine, norlupinane, octahydropyridocoline, and 1-azabicyclo[4.4.0]decane) was unknown prior to its discovery in the common lupin alkaloids: lupinine, cytisine, sparteine, lupanine, and anagyrine. In this respect quinolizidine has a history similar to that of its ring homolog, pyrrolizidine, which was unknown prior to its discovery in the *Senecio* alkaloids.

The lupin alkaloids are found most abundantly in genera within the Leguminosae family and especially within the Papilionaceae, leguminous sub-family, but certain of the lupin alkaloids are also found in the plants of other families, such as the Chenopodiaceae, Berberidaceae, and

TABLE 1
LUPIN ALKALOIDS

Alkaloid	Source	M.p., °C.	$[\alpha]_D$
Aloperine $C_{15}H_{24}N_2$	<i>Sophora alopecuroides</i> L. (1)	73–75	85.9° ^a
Ammodendrine $C_{12}H_{20}N_2O$	<i>Ammodendron conollyi</i> Bge. (2)	73–74 (Monohydrate)	±0°
Ammothamnine $C_{15}H_{24}N_2O_3$	<i>Ammothamnus lehmanni</i> Bge. (3)	199–201	±0°
Anagyrine $C_{15}H_{20}N_2O$ (Mono- lupine, rhombinine, alkaloid III (4))	<i>Anagryis foetida</i> Lour. (5, 6) <i>Baptisia minor</i> Lehm. (7) <i>Baptisia perfoliata</i> (L.) R. Br. (8) <i>Cytisus caucasicus</i> Hort. (9, 10) <i>Cytisus linifolius</i> Lam. (11) <i>Cytisus stenopetalus</i> Christ. (12, 13) <i>Genista humifusa</i> L. (13) <i>Genista tinctoria</i> L. (14) <i>Lupinus caudatus</i> Kellogg (15, 16) <i>Lupinus laxiflorus</i> var. <i>silvicola</i> C. P. Smith (17) <i>Lupinus macounii</i> Rydb. (18) <i>Lupinus pusillus</i> Pursh (19) <i>Sophora chrysophylla</i> Seem. (20) <i>Thermopsis lanceolata</i> R. Br. (4, 21) <i>Thermopsis rhombifolia</i> (Nutt.) Richards (22) <i>Ulex europaeus</i> L. (23)	b.p. 210–215 (4 mm.)	–165.3°
Aphyllidine $C_{15}H_{22}N_2O$	<i>Anabasis aphylla</i> L. (24, 25, 26, 27, 28, 29)	112–112.5	5.57° ^e
Aphylline $C_{15}H_{24}N_2O$	<i>Anabasis aphylla</i> L. (24, 25, 26, 27, 28, 29)	57	10.3° ^e
Baptifoline $C_{15}H_{20}N_2O_2$ (Alkaloid P3)	<i>Baptisia minor</i> Lehm. (7) <i>Baptisia perfoliata</i> (L.) R. Br. (8)	210	–147.7° ^a
Calycotamine $C_{11}H_{15(17)}NO_3$	<i>Calycotome spinosa</i> (L.) Link (30)		
d-Calycotomine $C_{12}H_{17}NO_3$	<i>Calycotome spinosa</i> (L.) Link (30) <i>Cytisus nigricans</i> var. <i>elonga-</i> <i>tus</i> Willd. (13)	139–141	21° ^b
dl-Calycotomine $C_{12}H_{17}NO_3$	<i>Calycotome spinosa</i> (L.) Link (30) <i>Cytisus proliferus</i> L. (31)		±0°

TABLE 1 (Continued)

Alkaloid	Source	M.p., °C.	$[\alpha]_D$
Cytisine $C_{11}H_{14}N_2O$ (Ulexine, baptitoxine, sophorine)	<i>Anagyris foetida</i> L. (5, 6)	155	-119.6 ^{ob}
	<i>Baptisia australis</i> (L.) R. Br. (12, 32)		
	<i>Baptisia exaltata</i> Sweet (33)		
	<i>Baptisia leucantha</i> Torr. and Gray (33)		
	<i>Baptisia minor</i> Lehm (7)		
	<i>Baptisia perfoliata</i> (L.) R. Br. (8)		
	<i>Baptisia tinctoria</i> R. Br. (34)		
	<i>Cytisus battandieri</i> Maire (12, 13)		
	<i>Cytisus canariensis</i> Maire (12)		
	<i>Cytisus hillebrandii</i> Briq. (12)		
	<i>Cytisus laburnum</i> L. (35)		
	(<i>Laburnum vulgare</i> J. Presl)		
	<i>Cytisus linifolius</i> Lam. (11)		
	<i>Cytisus monspessulanus</i> L. (13, 36)		
	<i>Cytisus stenopetalus</i> (12, 13)		
	<i>Genista aethnensis</i> D C. (37)		
	<i>Genista ferox</i> Poir. (13)		
	<i>Genista tinctoria</i> L. (14)		
	<i>Genista virgata</i> Link. (12, 13)		
	<i>Laburnum alpinum</i> J. Presl (38)		
	<i>Laburnum vulgare</i> J. Presl (38)		
	<i>Piptanthus nepalensis</i> Sweet (39)		
	<i>Sophora chrysophylla</i> Seem. (20)		
	<i>Sophora microphylla</i> Ait. (40)		
	<i>Sophora secundiflora</i> Lag. (35)		
	<i>Sophora tomentosa</i> L. (35)		
	<i>Spartium junceum</i> Lam. (41)		
	<i>Thermopsis lanceolata</i> R. Br. (42, 43)		
	<i>Thermopsis rhombifolia</i> (Nutt.) Richards (22)		
	<i>Ulex europaeus</i> L. (23, 38)		
Dilupine $C_{16}H_{26}N_2O_2$	<i>Lupinus barbiger</i> S. Wats. (44)		65.5 ^{ob}
Homothermopsine $C_{17}H_{24}N_2O$	<i>Lupinus lanceolata</i> R. Br. (4)	224-225	86.9 ^{od}

TABLE 1 (Continued)

Alkaloid	Source	M.p., °C.	$[\alpha]_D$
Hydroxylupanine $C_{15}H_{24}N_2O_2$ (Octa- lupine)	<i>Lupinus albus</i> L. (48) <i>Lupinus angustifolius</i> L. (49) <i>Lupinus hilarianus</i> Benth. (50) <i>Lupinus perennis</i> L. (51) <i>Lupinus polyphyllus</i> Lindl. (52) <i>Lupinus sericeus</i> var. <i>flexuosus</i> C. P. Smith (91, 309)	172-174	64.1° ^b
<i>d</i> - α -Isolupanine $C_{15}H_{24}N_2O$	<i>Lupinus caudatus</i> Kellogg (310) <i>Lupinus sericeus</i> R. Br. (311)	75-76	65.9° ^a
<i>d</i> - α -Isosparteine $C_{15}H_{26}N_2$ (Geni- steine)	<i>Lupinus caudatus</i> Kellogg (310) <i>Cytisus scoparius</i> Link. (45, 46, 312)	108-110	-51.3° ^a
Laburnine $C_8H_{15}NO$	<i>Cytisus laburnum</i> L. (313)	b.p. 80-90 (0.01 mm.)	15.45° ^a
<i>d</i> -Lupanine $C_{15}H_{24}N_2O$	<i>Cytisus austriacus</i> L. (13) <i>Cytisus caucasicus</i> Grossheim (9, 10) <i>Cytisus ratisbonnensis</i> Schaeff. (53) <i>Cytisus sessilifolius</i> L. (13) <i>Lupinus albus</i> L. (54, 55, 57, 60, 61) <i>Lupinus angustifolius</i> L. (54, 56, 58, 59, 62) <i>Lupinus arboreus</i> Sims. (63) <i>Lupinus caudatus</i> Kellogg (310) <i>Lupinus kingii</i> S. Wats. (64) <i>Lupinus laxus</i> Rydb. (65) <i>Lupinus perennis</i> L. (54) <i>Lupinus polyphyllus</i> Lindl. (52, 66) <i>Lupinus sericeus</i> R. Br. (311) <i>Podalyria sericea</i> R. Br. (67) <i>Virgilia capensis</i> Lam. (39)	44	61.4° ^c
<i>l</i> -Lupanine $C_{15}H_{24}N_2O$ (Hydro- rhombinine)	<i>Lupinus macounii</i> Rydb. (18, 68) <i>Lupinus pusillus</i> Pursh (19) <i>Podalyria buxifolia</i> Willd. (67) <i>Podalyria calyptata</i> Willd. (67)	44	-61 0° ^c

TABLE 1 (Continued)

Alkaloid	Source	M.p., °C.	$[\alpha]_D$
<i>dl</i> -Lupanine $C_{15}H_{24}N_2O$	<i>Lupinus albus</i> L. (54, 55) <i>Lupinus termis</i> Forsk. (69) <i>Podalyria buxifolia</i> Willd. (67) <i>Podalyria sericea</i> R. Br. (67) <i>Virgilia capensis</i> Lam. (39)	98–99	$\pm 0^\circ$
Lupinine $C_{10}H_{19}NO$	<i>Anabasis aphylla</i> L. (24, 70, 71, 72) <i>Lupinus luteus</i> L. (54, 73, 74, 75, 76) <i>Lupinus niger</i> Pharm. (54, 76, 77) <i>Lupinus palmeri</i> S. Wats. (78)	70–71	-20.9°_a -25.9°_b
Matrine $C_{15}H_{24}N_2O$ (Sopho- carpidine)	<i>Sophora alopecuroides</i> L. (1) <i>Sophora angustifolia</i> Sieb. & Zucc. (79) <i>Sophora flavescens</i> Ait. (80) <i>Sophora microphylla</i> Ait. (40) <i>Sophora pachycarpa</i> Schrenk. (80, 81, 82) <i>Sophora tetraptera</i> F. Mill. (83) <i>Sophora</i> species of the Chatham Islands (84) and Anawhata, N.Z. (85)	α 77 β 87 γ liq. δ 84	40.93 ^{ob}
3-Methoxypyridine C_6H_7NO	<i>Equisetum arvense</i> L. (86) <i>Thermopsis rhombifolia</i> (Nutt.) Richards (87)	b.p. 50° (1 mm.)	—
Methylcytisine $C_{12}H_{16}N_2O$ (<i>N</i> -Methylcytisine, caulophylline)	<i>Anagyris foetida</i> L. (5) <i>Baptisia australis</i> (L.). R. Br. (12, 32) <i>Baptisia minor</i> Lehm. (7) <i>Baptisia perfoliata</i> (L.) R. Br. (8) <i>Caulophyllum thalictroides</i> (L.) Michx. (88) <i>Cytisus canariensis</i> Maire (12) <i>Cytisus hillebrandii</i> Briq. (12) <i>Cytisus monspessulanus</i> L. (13, 36) <i>Cytisus stenopetalus</i> Christ. (12) <i>Genista tinctoria</i> L. (14) <i>Sophora microphylla</i> Ait. (40)	138	-221°

TABLE 1 (Continued)

Alkaloid	Source	M.p., °C.	$[\alpha]_D$
	<i>Sophora tetraptera</i> F. Mill. (83)		
	<i>Sophora</i> species of the Chatham Islands (84) and Anawhata, N.Z. (85)†		
	<i>Thermopsis lanceolata</i> R. Br. (4)		
	<i>Thermopsis rhombifolia</i> (Nutt.) Richards (22)		
Monspessulanine $C_{16}H_{22}N_2O$	<i>Cytisus monspessulanus</i> L. (36)	101	117° ^a
Oxymatrine $C_{15}H_{24}N_2O_2$	<i>Sophora angustifolia</i> var. <i>flavescens</i> S. and Z. (92)	208	47.7° ^a
Pentalupine $C_{16}H_{30}N_2O$	<i>Lupinus palmeri</i> Wats. (78)	b.p. 175-182 (2 mm.)	-3.20° ^a
Pusilline $C_{15}H_{28}N_2$ (Deriva- tives: Nonalupine, Spathulatine)	<i>Lupinus pusillus</i> Pursh (19) <i>Lupinus andersonii</i> Wats. (89, 309) <i>Lupinus sericeus</i> Pursh. (90, 309) <i>Lupinus marianus</i> Rydb. (90, 108, 309)	b.p. 100-110 (0.2 mm.)	-15.3° ^a
Retamine $C_{15}H_{26}N_2O$	<i>Genista aethnensis</i> D C. (37) <i>Retama sphaerocarpa</i> Boiss. (93, 94, 95, 96, 97)	168	43.15° ^a
Rhombifoline $C_{15}H_{20}N_2O_2$	<i>Thermopsis rhombifolia</i> (Nutt.) Richards (22)	Amorphous	
Sarothamnine $C_{30}H_{50}N_4$	<i>Cytisus scoparius</i> L. (98, 314)	173-174	-48.4° ^d
Sophocarpine $C_{15}H_{24}N_2O$	<i>Ammothamnus lehmanni</i> Bge. (3,100) <i>Sophora angustifolia</i> var. <i>flavescens</i> S. and Z. (80) <i>Sophora alopecuroides</i> L. (1) <i>Sophora pachycarpa</i> Schrenk. (99)	53-54	-29.4° ^a
Sophochrysin $C_{13-15}H_{21-19}N_3O_2$	<i>Sophora chrysophylla</i> Seem. (20) <i>Sophora microphylla</i> Ait. (40) <i>Sophora tetraptera</i> F. Mill. (83) <i>Sophora</i> species from the Chatham Islands (84)	284-287 (Amorphous)	-113.2° ^a
Sophoramine $C_{15}H_{20}N_2O$	<i>Sophora alopecuroides</i> L. (101)	164-165	-90.8° ^a

TABLE 1 (Continued)

Alkaloid	Source	M.p., °C.	$[\alpha]_D$
Sophoridine $C_{15}H_{26}N_2O$	<i>Sophora alopecuroides</i> L. (101)	109–110	–63.6° ^b
<i>d</i> -Sparteine $C_{15}H_{26}N_2$ (Pachycarpine)	<i>Ammodendron conollyi</i> Bge. (2) <i>Ammothamnus lehmanni</i> Bge. (3) <i>Anagyris foetida</i> L. (5) <i>Baptisia australis</i> (L.) R. Br. (32) <i>Baptisia minor</i> Lehm. (7) <i>Baptisia perfoliata</i> (L.) R. Br. (8) <i>Cytisus caucasicus</i> Hort. (9, 10) <i>Lupinus pusillus</i> Pursh (19) <i>Retama sphaerocarpa</i> Boiss. (95a) <i>Sophora pachycarpa</i> C. A. Mey. (81) <i>Thermopsis lanceolata</i> R. Br. (4, 21)	b.p. 98–100° (.2 mm.)	+17.1° ^a
<i>l</i> -Sparteine $C_{15}H_{26}N_2$ (Lupinidine)	<i>Chelidonium majus</i> L. (102) <i>Cytisus beanii</i> Nichols (103) <i>Cytisus grandiflorus</i> D C. (103) <i>Cytisus kewensis</i> Bean (103) <i>Cytisus proliferus</i> L. (31) <i>Cytisus ratibonnensis</i> Schaeff. (C. biflorus L'Hérit.) (53) <i>Cytisus scoparius</i> Link (103) <i>Cytisus versicolor</i> Briq. (103) <i>Genista aethnensis</i> D C. (37) <i>Lupinus arboreus</i> Sims. (63) <i>Lupinus barbiger</i> S. Wats. (44, 104) <i>Lupinus caudatus</i> Kellogg (310) <i>Lupinus laxus</i> Rydb. (65) <i>Lupinus luteus</i> L. (54, 75) <i>Lupinus mutabilis</i> Sweet. (105) <i>Lupinus niger</i> Pharm. (77) <i>Retama sphaerocarpa</i> Boiss. (93, 94, 95, 96, 97) <i>Sarothamnus scoparius</i> Koch (106) (= <i>Cytisus scoparius</i>) <i>Spartium junceum</i> L. (107) <i>Cytisus proliferus</i> L. (31)	b.p. 118° (18 mm.)	–17.0° ^a
<i>dl</i> -Sparteine $C_{15}H_{26}N_2$			

TABLE 1 (Continued)

Alkaloid	Source	M.p., °C.	$[\alpha]_D$
Tetralupine $C_{10}H_{19}NO$	<i>Lupinus palmeri</i> Wats. (78)	81–83	4.63 ^{ob}
<i>d</i> -Thermopsine $C_{15}H_{20}N_2O$ (Hexa- lupine)	<i>Lupinus caudatus</i> Kellogg (310) <i>Lupinus corymbosus</i> Heller (47, 315)	207	154.4 ^{oa}
<i>l</i> -Thermopsine $C_{15}H_{20}N_2O$	<i>Thermopsis lanceolata</i> R. Br. (4, 21, 43, 109, 110) <i>Thermopsis rhombifolia</i> (Nutt.) Richards (22)	206–206.5	–159.6 ^{oa}
Trilupine $C_{15}H_{24}N_2O_3$	<i>Lupinus barbiger</i> S. Wats. (44) <i>Lupinus laxus</i> Rydb. (65)	256–257	63.8 ^{ob}
Virgilidine $C_{10}H_{19}NO$	<i>Virgilia capensis</i> Lam. (39)	b.p. 90° (0.01 mm.)	12 ^{oa}
Virgiline $C_{16}H_{26}N_2O_2$	<i>Virgilia capensis</i> Lam. (39)	248	–46 ^{oa}
P1 $C_{15}H_{22}N_2O$ (?)	<i>Lupinus macounii</i> Rydb. (18)	126	
P2 $C_{11}H_{18}N_2O$ (?)	<i>Baptisia australis</i> (L.) R. Br. (32) <i>Baptisia perfoliata</i> (L.) R. Br. (8)	300	
P4	<i>Baptisia minor</i> Lehm. (7)		
“Base E”	<i>Sophora microphylla</i> Ait. (40)	168–171	
$C_{15}H_{20}N_2O_5$	<i>Ulex europaeus</i> L. (23)	170	
$C_{15}H_{24}N_2O$ (A mix- ture of <i>d</i> - and <i>dl</i> - lupanine)	<i>Virgilia capensis</i> Lam. (39) <i>Lupinus laxus</i> Rydb. (65)	b.p. 138–145° (0.01 mm.) 176–177	25 ^{oa} 133.2 ^{ob}
$C_{15}H_{24}N_2O_2$			

^a Ethanol^b Water^c Acetone^d Chloroform^e Methanol—solvent used in determination of specific rotation.

Papaveraceae. The distribution of these alkaloids is indicated in Table 1, from which it will be seen that a particular alkaloid may occur in different genera within the same botanical family and in different species within the same genus. Some species apparently contain a single alkaloid while other species contain up to six different alkaloids. Hybrids appear to contain the alkaloids found in the parent species. Some effort is being made, especially by White and Briggs in New Zealand, by Marion and Manske in Canada, and by Couch in the United States, to relate more satisfactorily the alkaloidal content and the taxonomical designation of the Papilionaceous plants. The work of White has also included an examination of the progressive movement of lupin alkaloid through the different organs during the life of a plant: from core to cortex, to the top of the plant, to flower parts, pods, and finally seeds.

II. Extraction Procedure

Since lupin seeds are used in some areas in cattle feeding, it is of practical as well as theoretical interest to determine the stage at which the seeds will be rich in the alkaloidal material responsible for toxicity. It has also been important to devise methods for the removal of alkaloids from the seeds so that the detoxified or "debittered" material can still be used as feed (111). Extraction procedures which accent the recovery of non-alkaloidal material have less interest to the alkaloid chemist than those which provide for the isolation of the pure organic bases. Given below are typical examples of the extraction procedures employed for the isolation of the lupin alkaloids: lupinine, cytisine, *l*-sparteine, *d*-lupanine, and anagryrine. The methods selected are representative of those utilized for the isolation of the less abundant or well-known lupin alkaloids as well. These methods are also representative of the different quantities of materials which are handled. One of the methods was selected (for anagryrine) to indicate some of the complexities of separation when there are a number of alkaloids present in a plant, rather than only one main alkaloidal constituent. The techniques of fractional distillation of the bases, fractional crystallization of alkaloid salts, such as perchlorates and picrates, and extractions dependent upon differential solubility have been employed for the isolation of pure individual alkaloids from a mixture.

Lupinine (78). *Lupinus palmeri* was air-dried and ground, and 60.9 kg. was extracted with ethanol. The solvent was distilled and the residual extract was boiled with successive portions of water until all soluble matter was removed. The concentrated aqueous solutions were treated with an excess of a mixture of neutral and basic lead acetates, filtered, and freed from the excess of lead with hydrogen sulfide. The filtrate was concentrated, made alkaline with sodium hydroxide, and extracted with chloroform. The solvent was distilled from the chloroform extract, leaving the

crude alkaloids in the form of a reddish sirup. The sirup contained nearly 25 % of its weight of chloroform, which was finally expelled by adding enough methanol to the mixture to form the azeotropic mixture which was distilled at 53.6°. The last traces of chloroform were removed by a repetition of this process. By this means 1668 g. of crude alkaloid was obtained. This alkaloid was repeatedly distilled *in vacuo* until there was obtained a colorless substance that yielded a colorless fluid on melting which solidified rapidly in the receiver. It was identified as lupinine, b.p. 160–163° (4 mm.), 269–270° (754.5 mm.), m.p. 68–69°, $[\alpha]_D^{26} - 25.93^\circ$ (water), $[\alpha]_D^{28} - 20.91^\circ$ (ethanol).

Cytisine (12, 38). The ground tops and seeds of *Laburnum vulgare* were air-dried and extracted in a soxhlet with 50 % aqueous ethanol to which had been added 2 % of acetic acid. The extract after concentration was cleared with lead acetate, concentrated, made alkaline with sodium hydroxide, and extracted six times with an equal volume of chloroform. This left only a trace of cytisine in the aqueous layer. When the chloroform was removed, the residual alkaloidal material crystallized in part. No clear-cut separation of components was accomplished by fractional crystallization of the free base or the crude picrate. The isolation of cytisine as the benzenesulfonyl derivative was effected according to the method of Ing (5), and benzenesulfonyl-cytisine was collected and recrystallized from ethanol as glistening prisms, m.p. 261°. Microchemical tests and picrate formation and identification were also used to establish the presence of cytisine in a particular plant.

l-Sparteine (44). Ground *Lupinus barbiger* (74.54 kg.) was extracted with ethanol. The solvent was distilled and the residual extract was boiled with successive portions of water until all soluble matter was removed. The combined and concentrated aqueous solutions were treated with an excess of a mixture of neutral and basic lead acetates, filtered, and freed from the excess of lead with hydrogen sulfide. The filtrate was concentrated, made alkaline with sodium hydroxide, and extracted with chloroform. The major portion of the solvent was removed by distillation from the chloroform extract and the final traces of chloroform by azeotropic distillation with methanol. The crude alkaloids were treated with an equal volume of ether, which dissolved nearly half. The dissolved alkaloids, freed from ether, were then dissolved in petroleum ether, which took up all but a trace of resinous matter. The clear petroleum ether solution was evaporated to give 441 g. of brownish sirup which gave a strong reaction for sparteine in the modified Grant test. The fraction which distilled under 195° at 1 mm. was dissolved in dilute hydrochloric acid, and aqueous mercuric chloride was added. The sparteine mercurichloride which separated was purified by recrystallization from hot 20 % hydrochloric acid. The alkaloid was recovered from this compound by treating it with aqueous ammonia and extracting with chloroform. When the solvent was removed, the base distilled at 185° (17 mm.), $n_D^{27} 1.5256$, $[\alpha]_D^{30} - 6.07^\circ$ (homogeneous).

d-Lupanine (64). Ground *Lupinus kingii* (12.18 kg.) was extracted by intermittent percolation with ethanol containing acetic acid. The solvent was removed from the percolate, the residue was mixed with water and precipitated with aqueous lead acetate. The filtrate was freed from lead with hydrogen sulfide and was concentrated to 1 liter. Alkalization with potassium hydroxide was followed by extraction with chloroform until the major portion of the alkaloid was removed. The solvent was distilled, leaving about 100 g. of red-brown sirup. This was digested with hot benzene, which dissolved the greater portion of it. When cooled, the benzene solution deposited a thin film, which was removed. Then the benzene was allowed to evaporate spontaneously from the solution to yield 74.5 g. (0.61 % of dry plant) of crude *d*-lupanine, identified as such and converted to a number of derivatives.

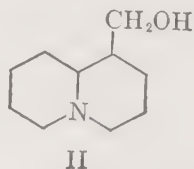
Anagyrine (8). *Baptisia perfoliata* (4285 g.) was dried, ground, and extracted in soxhlets with methanol. Removal of most of the methanol left a residue that was diluted with water, made acid to congo red with hydrochloric acid, and heated on the steam-bath for eight hours. The mixture was cooled and filtered with suction. The insoluble material was again heated with dilute hydrochloric acid, cooled, and filtered. The combined filtrate was extracted repeatedly with ether, after which the aqueous solution was alkalized with ammonia. The ammoniacal mixture was extracted with chloroform in a continuous liquid-liquid extractor. The chloroform extract was evaporated to dryness and the residual bases were warmed with dilute hydrochloric acid. The cooled acidic solution was filtered through charcoal, repeatedly extracted with ether, alkalized with ammonia, and extracted with chloroform in a continuous liquid-liquid extractor. The chloroform extract, on evaporation to dryness, yielded the crude bases as a soft brown gum (8.0 g.). The crude alkaloid was fractionated *in vacuo* into the following fractions: I, b.p. 100–125° (0.2 mm.), 0.95 g. of colorless oil; II, b.p. 135–150° (0.2 mm.), 0.82 g. of partly crystalline colorless oil; III, b.p. 150–165° (0.2 mm.), 0.3 g. of a thick oil which crystallized on cooling; IV, b.p. 165–180° (0.2 mm.), 0.86 g. of a mixture of crystals and yellow oil; V, b.p. 180–200° (0.2 mm.), 0.14 g. of viscous yellow oil; and undistilled residue. *d*-Sparteine was isolated from fraction I; cytisine, from fraction II, III, and IV; N-methyleytisine, from fraction II. Some anagyrine was carried over with cytisine in fraction IV but the major portion of it was found in fraction V, which was dissolved in methanol and the solution was made just acid to congo red by the cautious addition of 65 % perchloric acid. The crystalline anagyrine perchlorate thus obtained was recrystallized several times from boiling methanol, from which it separates as colorless needles; m.p. 315°. An aqueous solution of the perchlorate was made ammoniacal and extracted with chloroform. The base, obtained by removal of the chloroform, was dissolved in methanol and added to a methanolic solution of picric acid. Anagyrine picrate separated as yellow needles; m.p. 252°.

The structure of the alkaloids will be considered in the above order of increasing complexity. Related and isomeric alkaloids will be discussed within these five main groups: lupinine, cytisine, sparteine, lupanine, and anagyrine.

III. Structure of the Alkaloids

1. LUPININE, $C_{10}H_{19}NO$

Lupinine (II), isolated from yellow lupin seeds by Cassola (112) in 1835, was obtained in pure form by Baumert in 1881. Derivatives



were obtained (113), including the ethiodide, which indicated the presence of a basic nitrogen. The salts which are currently considered useful

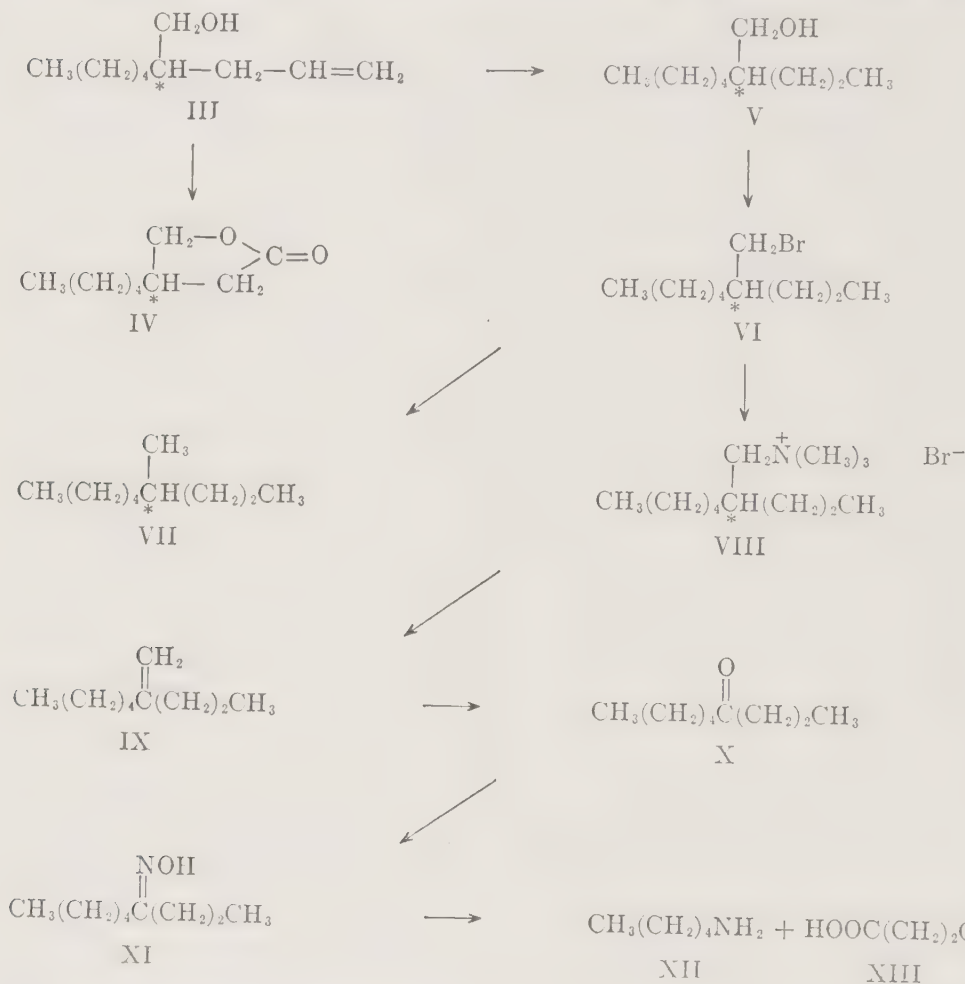
for the characterization of lupinine are as follows (78): hydrochloride, m.p. 207–209°; hydriodide, 140–141°; methiodide, 295–296°; methochloride, 212–213°; picrate, 136–137° or 196–197°; *d*-camphorsulfonate, 181–182°; aurichloride, 211–213°; platinichloride, 166–166.5°. Further early characterization of lupinine and attempts at dehydration of lupinine with hydrochloric acid and phosphorus pentoxide were carried out by Baumert (114, 115, 116, 117) and by Schmidt and his coworkers (54, 73, 77). Schmidt and Berend (73) obtained an acetyl derivative and found that a chlorine containing product was obtained upon treatment of lupinine with phosphorus pentachloride or oxychloride.

a. The Structure of Lupinine. The correct molecular formula for lupinine, $C_{10}H_{19}NO$, was assigned by Willstätter and Fourneau (118) in 1902, in a reinterpretation of the earlier work, mainly that of Baumert, and it was realized that the only functional groups present in the molecule were a tertiary nitrogen atom and a carbinol. The presence of the hydroxyl group was firmly established by the formation of a benzoyl derivative (m.p. 49–50°) and a phenylurethane (m.p. 94–95°) and by the dehydration of lupinine to anhydrolupinine, $C_{10}H_{17}N$, by means of sulfuric acid. Anhydrolupinine, b.p. 216.5–217.5° (726 mm.), was characterized by the formation of derivatives: methiodide, m.p. 180°; aurichloride, 140–141°; platinichloride, 216°. The fact that the hydroxyl function was primary was indicated by the oxidation (118) of lupinine with chromic anhydride to lupininic acid, $C_9H_{16}N\cdot COOH$, m.p. 255° (hydrochloride, m.p. 275°; aurichloride, 188°; platinichloride, 235°); methyl ester, b.p. 131° (15 mm.) (methiodide, m.p. 225–226°; platinichloride, 210–212°).

The presence of a bicyclic nitrogen ring system in lupinine was also established by Willstätter and Fourneau (118), who carried out a Hofmann exhaustive methylation on the alkaloid and found that it required three degradation stages to produce trimethylamine and an unsaturated alcohol. The Hofmann exhaustive methylation procedure was also followed by Karrer and his coworkers (119), modified in that hydrogenation followed each degradation stage. The final unsaturated alcohol, $C_{10}H_{20}O$, contained the original primary alcohol group and a terminal double bond. The position of the double linkage was established by the stepwise oxidation of the $C_{10}H_{20}O$ molecule, first with zinc permanganate to a glycol and then with chromic anhydride and sulfuric acid to formic acid and a stable lactone, $C_9H_{16}O_2$; b.p. 253–255°. The observed stability would imply that $C_9H_{16}O_2$ was either a γ - or a δ -lactone and therefore that the hydroxyl group had to be attached to the γ - or δ -carbon atom with respect to the second unsaturated carbon. Both the unsaturated alcohol and the saturated alcohol, $C_{10}H_{22}O$, derived from it had

measurable optical activity. This fact indicated that at least one asymmetric center in the molecule withstood the degradation process.

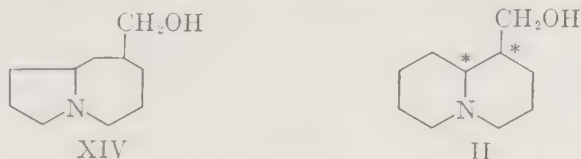
The saturated alcohol, $C_{10}H_{22}O$, was converted by phosphorus pentabromide (119) to an alkyl bromide $C_{10}H_{21}Br$, which was reduced



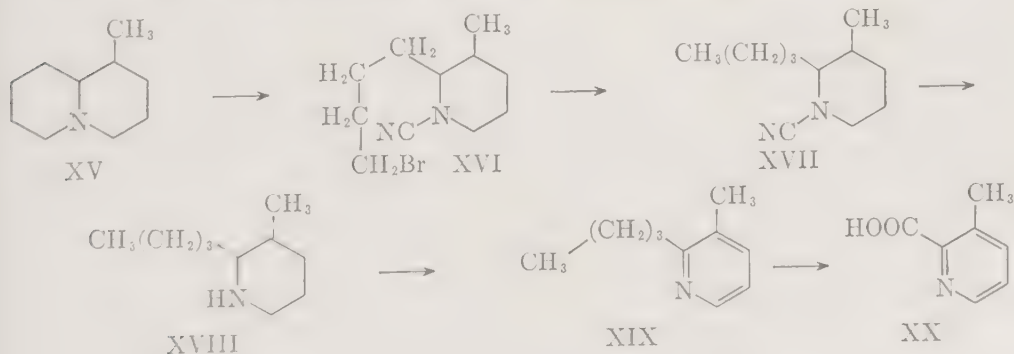
with zinc dust (and platinum chloride) to a saturated hydrocarbon, $C_{10}H_{22}$. The bromo compound could also be converted to an unsaturated hydrocarbon, $C_{10}H_{20}$, by treatment with trimethylamine followed by treatment with silver oxide. Since the unsaturated hydrocarbon was optically inactive there could be no asymmetric center in the C_8H_{18} residue of the unsaturated hydrocarbon: $C_8H_{18} > C = CH_2$. It was thereby established that the only asymmetric carbon in the original alcohol was that adjacent to the primary carbinol group. The unsaturated hydrocarbon, $C_{10}H_{20}$, was converted by ozonolysis to an optically inactive ketone, $C_8H_{18}CO$, which formed a crystalline semicarbazone, m.p. 60–61°. The oxime, although not obtained crystalline, was sub-

jected to a Beckmann rearrangement (concentrated sulfuric acid) and the resulting amide was hydrolyzed with hydrochloric acid to *n*-amylamine (XII) and *n*-butyric acid (XIII). The Beckmann rearrangement products established the structure of the oxime as XI and the structure of the ketone as X. The nonanone from lupinine was also compared directly with a sample of *n*-amyl *n*-propyl ketone (X), b.p. 75–76° (20 mm.), synthesized by an unequivocal method (caproyl chloride + *n*-propylzinc iodide).

With the structure of the ketone established unequivocally as 4-nonanone (X), the structures of the precursors (V, VI, VII, VIII, IX) were also definitely established. The assignment of structure III, 4-hydroxymethyl-1-nonene, to the original unsaturated alcohol was consistent with its stepwise conversion to X and its oxidation to the γ -lactone IV. With the realization that 4-hydroxymethyl-1-nonene was the product of the three-stage Hofmann degradation—with hydrogenation—of lupinine, there remained the problem of accommodating the nitrogen atom in the molecule so as to recreate the original bicyclic base. Karrer, Canal, Zohner, and Widmer (119) neglected as unlikely any structure which had three- or four-membered rings, and they indicated that structure XIV, with fused five- and seven-membered rings, was less likely than structure II, with fused six-membered rings as present in the berberine alkaloids. Their proposal of structure II for lupinine has been amply checked by other degradative work and finally by synthesis.

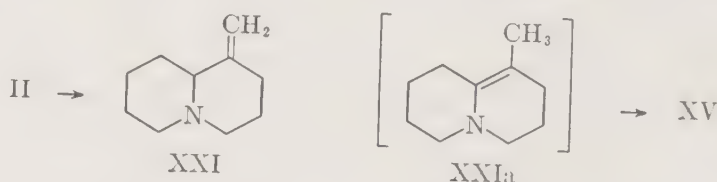


The structure of lupinine (II) was confirmed by Winterfeld and Holschneider (120) by means of a cyanogen bromide degradation of lupinane (XV) to 1-cyano-2-(ω -bromobutyl)-3-methylpiperidine (XVI). Lupinane (XV) was obtained from *pure* lupinine by sulfuric acid degrada-



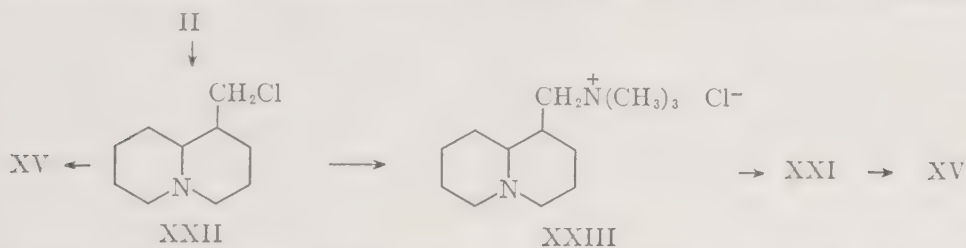
tion to anhydrolupinine, followed by hydrogenation over palladium on calcium carbonate. Treatment with cyanogen bromide gave a liquid bromolupinane cyanamide (XVI), from which the bromine was eliminated by hydrogenolysis over palladium on calcium carbonate in methanolic potassium hydroxide solution. The lupinane cyanamide (XVII) was hydrolyzed with hydrochloric acid to the secondary amine, $C_{10}H_{21}N$ (XVIII), b.p. 169–171° (hydrochloride, m.p. 151–153°; hydrobromide, m.p. 168–170°; β -naphthalenesulfonyl derivative, m.p. 86–87°). Dehydrogenation of XVIII produced a pyridine base, $C_{10}H_{15}N$ (XIX), b.p. 153–154° (platinichloride, m.p. 190–191°), which was oxidized by potassium permanganate to β -methylpicolinic acid, $C_7H_7NO_2$ (XX) (platinichloride, m.p. 189–190°), and quinolinic acid. Both acids were known compounds so that direct comparisons could be made. The loss of three carbons in the oxidation step ($XIX \rightarrow XX$) located the butyl group in compound XIX on the α -carbon, and the assignment of the structures XVII and XVI to its precursors and finally of the structure XV to lupinane followed logically.

The formula II for lupinine possesses two asymmetric carbon atoms, so that two racemates or four optically active forms with this structure would normally be expected. *Cis*- and *trans*-forms at the ring fusion, as in decalin, would not be expected due to the mobility of the electron pair on the nitrogen atom. The problem of establishing the existence of two asymmetric centers in the lupinine molecule was germane to the absolute proof that structure II represented the alkaloid, and accordingly this problem was attacked in a number of laboratories. Schöpf and Thomä (121) prepared anhydrolupinine (XXI) according to the method of



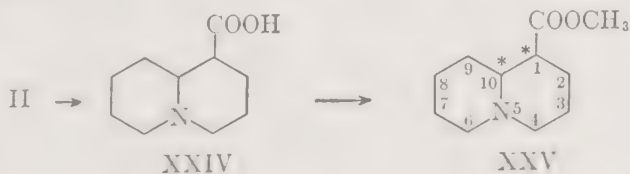
Willstätter and Fourné (118) and found that their product was optically inactive. The loss of activity may have been inherent in the method of dehydration. A product could have been produced which would equilibrate between XXI and the structure XXI_a, in which the second asymmetric carbon would also be destroyed. Hydrogenation of anhydrolupinine (121) over palladium on calcium carbonate according to the method of Bartholomäus and Schaumann (122) gave two isomeric, optically inactive lupinanes (XV), $C_{10}H_{19}N$, separated by the fractional crystallization of their picrates from methanol: α -lupinane picrate, m.p. 187°; β -lupinane picrate, m.p. 163°. Karrer and Vogt (123) were able

to prepare an optically active anhydrolupinine from the alkaloid through the intermediate chlorolupinane (XXII), (124, 125). Chlorolupinane,



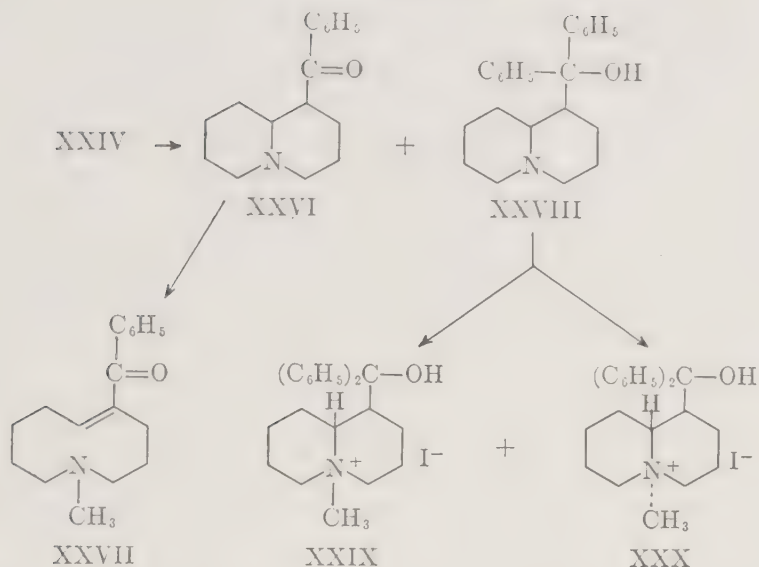
obtained in 85% yield by treatment of lupinine with thionyl chloride, was levorotatory, $[\alpha]_D^{20} - 32.9^\circ$ (ethanol). It was converted to the quaternary salt XXIII, $[\alpha]_D^{20} - 17.9^\circ$ (ethanol), by treatment with trimethylamine, and thence to anhydrolupinine (XXI) $[\alpha]_D^{23.5} - 49.8^\circ$ (homogeneous), by means of silver oxide and heat. Reduction of the levorotatory anhydrolupinine to lupinane by hydrogen over platinum oxide caused a diminution in specific rotation. That observed for the reduced product, lupinane (picrate, m.p. 185°), was $[\alpha]_D^{23} - 0.65^\circ$ (homogeneous). It was apparent that catalytic hydrogenation of the optically active anhydrolupinine (still possessing one asymmetric center) did not take place asymmetrically. A lupinane with higher specific rotation, $[\alpha]_D^{20} - 9.4^\circ$ (methanol), was obtained (123) directly from chlorolupinane (XXII) by means of sodium and ethanol. The picrate of this lupinane also melted at 185° and did not depress the melting point of the picrate of the less optically active lupinane. Both were of the α -lupinane type. The compound ψ -anhydrolupinine, $C_{10}H_{17}N$, $[\alpha]_D - 35.3^\circ$ (acetone) (picrate, m.p. 154°), prepared by Clemo and Raper (126) is of unknown structure since it was obtained by silver oxide degradation of chlorolupinine (XXII) methiodide.

The results obtained with the anhydrolupinines and lupinanes indicated that there were two asymmetric centers in the lupinine molecule. The same conclusion was reached in studies on the isomerization of lupinic acid (XXIV) esters. Natural lupinine is levorotatory. Methyl lupinate (XXV) made by Schöpf and Thomä (121) according to the directions of Willstätter and Fourneau (118) was obtained which varied from $[\alpha]_D^{21} - 19.4^\circ$ to $+5.8^\circ$ (methanol) in different batches. The most levorotatory sample of ester, methyl (–)lupinate, formed a non-crystalline picrate, the rotation of which was useful for identification



purposes; $[\alpha]_D^{16} - 41.8^\circ$ (chloroform). Hydrolysis of this ester with hydrochloric acid produced (–)lupininic acid hydrochloride, m.p. 275° , identical with the Willstätter-Fourneau compound (118), $[\alpha]_D^{21} - 13.1^\circ$ (methanol) (121). When this acid hydrochloride was treated with benzoyl chloride—phosphorus pentachloride followed by methanol, an epimeric ester, known as methyl (+)*epi*-lupininate, $[\alpha]_D^{16} + 54.8^\circ$ (methanol) resulted. Optical purity was achieved by purification through the picrate, m.p. 185° , $[\alpha]_D^{17} + 61.8^\circ$ (chloroform) (compare methyl (–)lupininate picrate). Derivatives of the (+)*epi*-lupininic acid were made (121): hydrochloride, m.p. 235° , $[\alpha]_D + 27.2^\circ$ (methanol) (127); amide, $C_{10}H_{18}N_2O$, m.p. 228° , $[\alpha]_D^{18} + 41.3^\circ$ (methanol); nitrile hydrochloride, $[\alpha]_D^{20} + 52.9^\circ$ (chloroform). The -19.4° and $+54.8^\circ$ esters are diastereoisomers or, more accurately, epimers (121). They possess identical configuration at C-10 but opposite configurations at C-1. It was found by Winterfeld and Holschneider (120) that methyl (–)lupininate was reduced by sodium and alcohol to an isomer of lupinine, m.p. $76-78^\circ$, $[\alpha]_D + 38.17^\circ$. The interpretation of this conversion applied by Schöpf, Schmidt, and Braun (127) was that the ester had first undergone epimerization in the alkaline solution and that the (+)*epi*-ester thus formed had undergone normal Beauveault-Blanc reduction to (+)*epi*-lupinine, the epimer of lupinine. They also considered that simultaneous epimerization and reduction could occur. Direct conversion of (–)lupinine to (+)*epi*-lupinine was realized by Winterfeld and Holschneider (120) (and interpreted by Schöpf and his coworkers (127)). Sodium in refluxing benzene changed (–)lupinine (natural lupinine) in three days to the dextrorotatory isomer. That epimerization had occurred was indicated by the facts that the (+)*epi*-lupinine was unchanged by sodium under the same conditions and that the (+)*epi*-lupinine was oxidized to a dextrorotatory isomer of lupininic acid. The melting point of a mixture of (–)lupinine, m.p. $68-69^\circ$, and (+)*epi*-lupinine, m.p. $76-78^\circ$, was $40-42^\circ$ (120). The remaining two optically active isomers of II would be enantiomorphic, taken individually, with these -23.52° and $+38.17^\circ$ compounds.

An interesting confirmation of the β -relationship of the amine and alcohol functions in lupinine was provided by Schöpf and his coworkers (127, 128). The ketone XXVI, b.p. $126-128^\circ$ (1 mm.) (picrate, m.p. 185° , $[\alpha]_D^{21} + 38.5^\circ$ (chloroform); methopicrate, m.p. $153-154^\circ$), was prepared either by the action of phenylmagnesium bromide on lupininic ester or by a Friedel-Crafts reaction between lupininic acid chloride and benzene. The high dextrorotation of the ketone (or its picrate) is consistent with the expected epimerization of the ester in the presence of the basic Grignard reagent and the epimerization of the acid during the process of formation of the acid chloride. The methiodide of the ketone

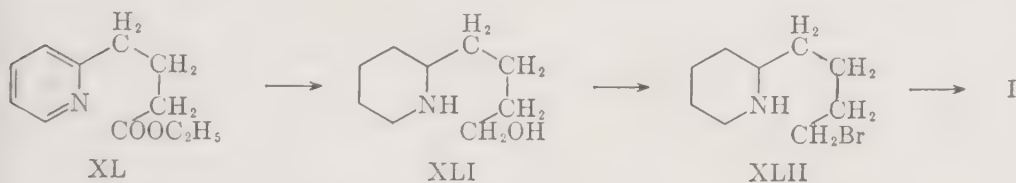


XXVI, when subjected to a Hofmann degradation, gave a single, pure *des*-base, $\text{C}_{17}\text{H}_{23}\text{NO}$ (XXVII), b.p. $143\text{--}145^\circ$ (1 mm.) (picrate, m.p. $142\text{--}143^\circ$; picrate of dihydro-*des*-base, m.p. $159\text{--}160^\circ$). The formation of a single product, an α,β -unsaturated ketone, in such degradation is typical of a β -aminoketone (129) and thus the result confirmed the structure already advanced for the β -aminoalcohol, lupinine. Also of theoretical interest was the carbinol XXVIII obtained by the Grignard reaction of phenylmagnesium bromide on either lupininic ester (128) or (+)*epi*-lupininic acid hydrochloride (127). The carbinol was obtained as a single pure compound, $\text{C}_{22}\text{H}_{27}\text{NO}$, m.p. $170\text{--}171^\circ$, $[\alpha]_{\text{D}}^{21} + 79.2^\circ$ (hydrobromide, m.p. 205°). In this compound the asymmetric centers at C-1 and C-10 were considered fixed and unique. In the formation of a methiodide, it was considered by Schöpf, Schmidt, and Braun (127) that a new asymmetric center would be introduced into the molecule—at the nitrogen. Two methiodides should thus be capable of existence, one in which the $\text{C}_{10}\text{—H}$ and the $\text{N}_5\text{—CH}_3$ are *cis* (XXIX) and one in which the $\text{C}_{10}\text{—H}$ and the $\text{N}_5\text{—CH}_3$ are *trans* (XXX). *Cis-trans* isomers would not be expected for a compound with a tertiary nitrogen at the bridge-head (see above), but their existence in a structure having a quaternary nitrogen at the bridge-head was confirmed experimentally by the isolation (127) of two pure methiodides, m.p. $250\text{--}252^\circ$ and m.p. 140° (the latter in hydrated form), from the carbinol XXVIII. This principle is important in consideration not only of lupinine but of all other lupin alkaloids containing the quinolizidine (I) ring system.

b. Synthesis of Norlupinane (Quinolizidine). The degradative work on lupinine and the work directed toward its synthesis met first at an

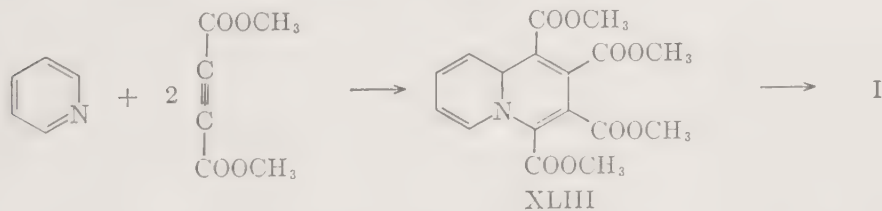
approach was the condensation of ethyl picolinate (XXXIII) with 1-methyl-2-pyrrolidone (XXXIV) in the presence of sodium ethoxide to give XXXV. This β -ketoamide was hydrolyzed to α -pyridyl γ '-methyl-aminopropyl ketone, from which the benzoyl derivative XXXVI was produced. Four moles of hydrogen were absorbed by XXXVI in acetic acid solution over platinum oxide, corresponding to reduction of the pyridine ring and the ketone group. Treatment of XXXVII with phosphorus pentabromide produced 1- α -piperidyl-1,4-dibromobutane (XXVIII), which underwent intramolecular alkylation to produce impure 1-bromoquinolizidine (XXXIX). Hydrogenolysis of XXXIX gave quinolizidine (I), identical in every way with norlupinane obtained from the alkaloid source, lupinic acid (130, 132).

Another synthesis of quinolizidine is due to the work of Clemo, Ramage, and Raper (133). Ethyl γ -2-pyridylbutyrate (XL) was

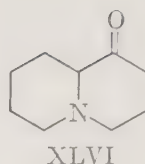
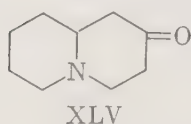
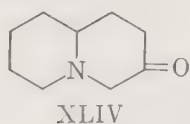


reduced to 4- α -piperidyl-1-butanol (XLI) by means of sodium and ethanol. The crude 4- α -piperidyl-1-bromobutane (XLII) produced on treatment of XLI with phosphorus pentabromide was converted to quinolizidine (I) (picrolonate, m.p. 245°) by intramolecular alkylation. Direct comparison of derivatives indicated that the synthetic and naturally-derived norlupinane were identical.

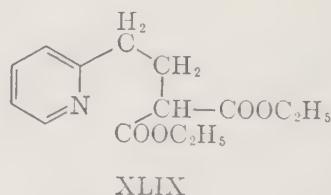
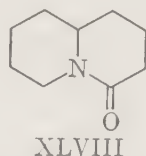
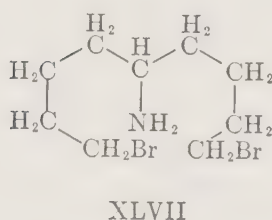
There followed other interesting methods of synthesis of norlupinane (quinolizidine). Diels and Alder (134) obtained impure quinolizidine on degradation, followed by hydrogenation, of the adduct of pyridine and dimethyl acetylenedicarboxylate (XLIII), and later (135) obtained the



pure compound by purification through the picrate. Clemo and his coworkers obtained the compound from a number of readily available precursors by a process which involved reduction of a ketoquinolizidine as the ultimate step and Dieckmann ring closure as the penultimate one.

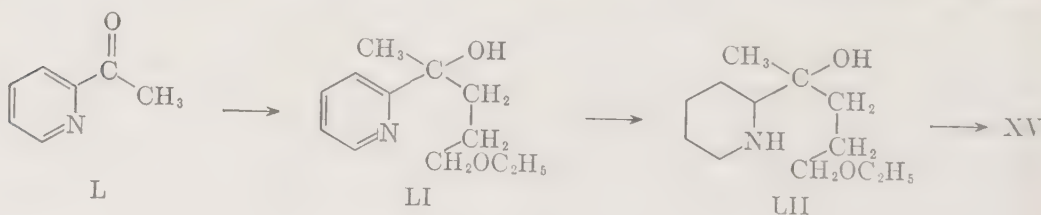


Clemmensen reduction of 2-ketoquinolizidine (XLV) produced quinolizidine (137). 1-Ketoquinolizidine (XLVI) (130) and 3-ketoquinolizidine (XLIV) (136, 316) exhibited unusual behavior in this reduction procedure, the Wolff-Kishner reduction (XLVI) proceeding normally to quinolizidine (137), but the product (130) of the Clemmensen reduction of this α -amino-ketone has been shown to be a structural isomer of quinolizidine, 1-azabicyclo[5.3.0]decane (picrate, m.p. 213–214°; picrolonate, 191.5°; methiodide, 282.5–283°) (138). More recently, quinolizidine has been synthesized by intramolecular dialkylation of 5-amino-1,9-dibromononane (XLVII) (139) according to the general method which Prelog and his coworkers have developed for the formation of bicyclic compounds possessing a bridge-head nitrogen. Galinovsky and Stern (140) succeeded in reducing the 4-ketoquinolizidine (XLVIII), first prepared by



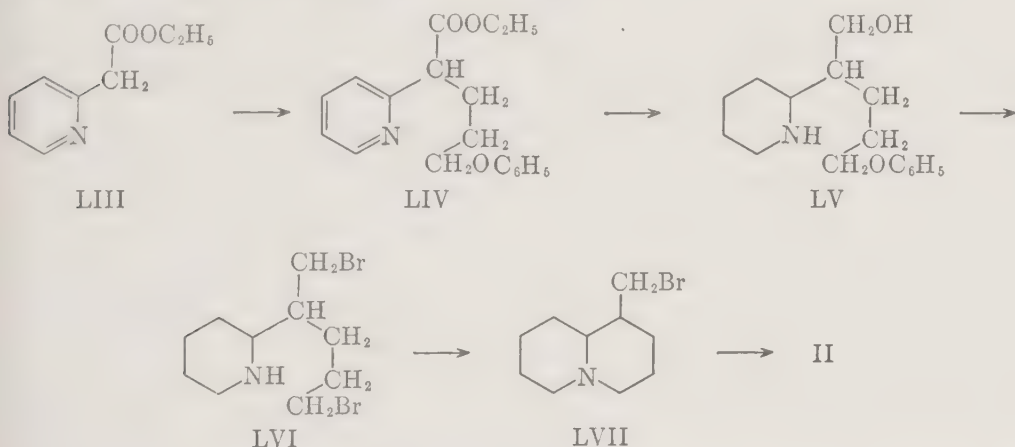
Clemo, Ramage, and Raper (133), to quinolizidine by an electrolytic method and by hydrogenation over platinum oxide in acetic acid solution. Boekelheide and Rothchild (141) effected the same change by hydrogenation of XLVIII over copper chromite at high temperature and pressure, and also converted the Michael adduct of malonic ester and 2-vinylpyridine (XLIX) (142) to quinolizidine by copper chromite hydrogenation (141, 143).

A closer approach to the synthesis of lupinine was made by Winterfeld and Holschneider (144, 145) in their synthesis of β -lupinane (see p. 135) (XV). 2-Acetylpyridine (L) was converted to the pyridyl carbinol



LI by reaction with γ -ethoxypropylmagnesium bromide. Reduction to the piperidyl carbinol LII was followed by treatment with hydriodic acid. The base produced, $C_{10}H_{19}N$, formed a picrate, m.p. 163° , and an aurichloride, m.p. $142-143^\circ$. The melting points were undepressed when the derivatives were mixed with the corresponding derivatives of inactive β -lupinane (XV) obtained from natural lupinine (120). The total synthesis of lupinine itself was achieved somewhat later by Clemo, Morgan, and Raper (146, 147).

c. Synthesis of Lupinine. The possible biosynthesis of lupinine from aminovaleric aldehyde (from lysine) has been mentioned by Schöpf, and by Anet, Hughes, and Ritchie (127, 148, 317). The laboratory synthesis of lupinine by Clemo, Morgan, and Raper (146) utilized ethyl 2-pyridylacetate (LIII) as a precursor:



Condensation of LIII with γ -phenoxypropyl bromide in the presence of potassium produced ethyl δ -phenoxy- α -2-pyridylvalerate (LIV), which was converted to the carbinol LV by hydrogenation over platinum oxide in acetic acid, followed by sodium and ethanol reduction. The carbinol was treated with fuming hydrobromic acid, and the intermediate amine dibromide (LVI) was further treated with alkali followed by phosphorus pentabromide. Two racemates of 1-bromomethylquinolizidine (LVII) were isolated by fractional crystallization of the picrolonates (m.p. 202° and 169°) from ethanol and regeneration of the bases. Each racemate of 1-bromomethylquinolizidine was converted to the corresponding form of 1-hydroxymethylquinolizidine (II) by boiling in aqueous sodium acetate. One of the forms obtained was *dl*-lupinine, m.p. 59° (picrate, m.p. 127° ; picrolonate, 203° ; methiodide, 303°), and the other *dl-epi*-lupinine (*cf.* 120, 127), m.p. 81° (picrate, m.p. 139° ; picrolonate, 225° ; methiodide, 248°). *dl*-Lupinine was resolved (147) by means of tartaric acid and the *l*-lupinine *d*-tartrate, m.p. 167° , $[\alpha]_D$

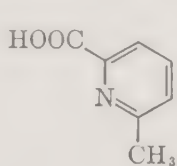
$14.9^\circ \pm 0.5^\circ$ (ethanol), thus obtained was identical with the *d*-tartaric acid salt of the natural alkaloid, m.p. 170° , $[\alpha]_D 15.5^\circ \pm 0.5^\circ$ (ethanol). The synthetic resolved base which was liberated from the salt melted at $69-70^\circ$ ($[\alpha]_D - 20.4^\circ$ (ethanol)) and did not depress the melting point of authentic lupinine of $[\alpha]_D - 21.3^\circ$ (ethanol). *d*-Lupinine *l*-tartrate, m.p. $167-168^\circ$, $[\alpha]_D - 15.8^\circ$ (ethanol), was also obtained, and from this salt *d*-lupinine, m.p. 68° , $[\alpha]_D 19.9^\circ$ (ethanol) was liberated.

The synthesis of *dl*-lupinine was also accomplished by Winterfeld and von Cosel (149) by a process similar to that which had been employed in the earlier synthesis of lupinane (144, 145) (see $\text{LI} \rightarrow \text{LII} \rightarrow \text{XV}$), but using α -hydroxyacetylpyridine in place of α -acetylpyridine (L). The product, *dl*-lupinine, was characterized as the picrolonate, m.p. 179° . The melting point observed was lower than that reported for the *dl*-lupinine picrolonate by Clemo and his coworkers (146).

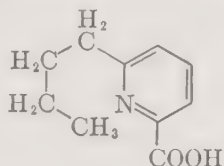
The compound of oxidation state intermediate between that of lupinine and lupinic acid, namely, lupinal, $\text{C}_{10}\text{H}_{17}\text{NO}$, m.p. $93-96^\circ$, has been obtained by Zaboev (72) through the use of chromic anhydride in acetic acid. It appears that the first use of natural lupinine itself as a synthetic tool dates from the work of Bartholomäus and Schaumann, described in two patents (150, 151). Products were characterized which resulted from the condensation of chloro- or bromo-lupinane (derived from lupinine (124, 125)) with ammonia, aniline, methylamine, dimethylamine, and piperidine (150). The product resulting from chlorolupinane and piperidine was also described by Clemo and Raper (126). Compounds of possible therapeutic interest were made by the condensation of a halolupinane with 8-amino-2-methylquinoline, 4-amino-2-methylquinoline, and by the combination of methylaminolupinane with 4-chloro-6-methoxy-2-methylquinoline, and aminolupinane with 2-chloro-6-methoxyquinoline and substituted 9-chloroacridines (151). Of special interest because of their antimalarial action were 6-methoxy-8-lupinylaminoquinoline and 2-methoxy-6-chloro-9-lupinylaminoacridine, synthesized by Knunyants and Benevolenskaya (152). 5-Methoxy-7-lupinylaminobenzothiazole did not have any therapeutic activity against avian malaria (152), nor did 11-(4-diethylamino-1-methylbutylamino)-lupinane (153). Lupinylbarbituric acid was also made for pharmacological testing by condensation of chlorolupinane with diethyl malonate, followed by reaction with urea (154). Esters of lupinine have been made, including nicotinylupinine (155) and *p*-aminobenzoyllupinine (156). The *p*-aminobenzoyl ester was found to possess marked local anesthetic action (156, 157) and has been called lupicaine (157, 158).

d. Isomers of Lupinine. The cyanogen bromide degradation of pure lupinine, m.p. $68-69^\circ$, had resulted (see p. 134) in the ultimate formation

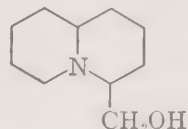
of β -methylpicolinic and quinolinic acids (120, 159). If the same process was followed with Merck's crude lupinine, m.p. 63–65° (120), two additional pyridine carboxylic acids were obtained at the final stage: α -methylpicolinic acid (LVIII) and α -*n*-butylpicolinic acid (LIX). Winterfeld



LVIII



LIX



LX

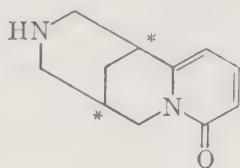
and Holschneider (120) considered these products to be evidence of the presence in crude lupinine of an isomer (since they could not result from lupinine), to which they assigned the formula LX and the name *allo*-lupinine. Winterfeld and Holschneider were able to synthesize a *dl*-*allo*-lupinine (4-hydroxymethylquinolizidine), m.p. 123–125°, which gave a crystalline mercurichloride, m.p. 201°, and reineckate, m.p. 152–153° (160, 161). The compound without the hydroxyl group, *allo*-lupinane (4-methylquinolizidine), has been synthesized by Lukes and Sorm (162). Two isomeric picrates, m.p. 187° and 195°, were isolated by means of their differential solubility in ethanol, corresponding to the two racemates expected for *allo*-lupinane. In the synthesis of 4-methylquinolizidine by Boekelheide and Rothchild (141), the only picrate obtained for characterization of the base, C₁₀H₁₉N, melted at 191–195°.

Tetralupine, m.p. 81–83°, [α]_D²⁰ 4.63° (water), is an alkaloid isomeric with lupinine found in *Lupinus palmeri* W. (78). The *d*-camphorsulfonic acid salt, m.p. 164–165°, [α]_D³⁰ 18.18° (water), depressed the melting point of (–)lupinine *d*-camphorsulfonate. Tetralupine depressed the melting point of (+)*epi*-lupinine (120, 127). The alkaloid is therefore not identical with either lupinine or *epi*-lupinine. Couch (78) suggested that it might be the *allo*-lupinine (LX) postulated as an alkaloidal contaminant of lupinine (120).

Virgilidine, [α]_D 12° (ethanol) is another naturally occurring isomer of lupinine (39). The picrate, m.p. 203°, and methiodide, m.p. 256–259°, were not identical with those of lupinine (*d* or *l*). The rotation of the base was different from that of (+)*epi*-lupinine and tetralupine, and virgilidine was, unlike these isomers, a liquid. In the microchemical slide reactions of virgilidine, there was observed a similarity to lupinine (39).

2. CYTISINE, C₁₁H₁₄N₂O

Cytisine (LXI), which has an additional nitrogen atom in the form of a bridged ring, was first isolated in the pure state by Husemann and Marmé (163). The quinolizidine ring (I) is present in this alkaloid



LXI

also, but here it occurs partially unsaturated. Derivatives of cytisine (also described as ulexine, baptitoxine, sophorine), which are useful for characterization or identification purposes are: picrate, m.p. 288–289° (7); aurichloride, 218–220° (20); perchlorate, 296° (20); picrolonate, 270°; *N*-acetyl, 209° (38); *N*-nitroso, 174° (164); methylenedicytisine, 212° (165); product with carbon disulfide, 197–198° (166); *N*-benzoyl, 116° (166). The *N*-methyl derivative, m.p. 138°, which can be obtained by the treatment of cytisine with methyl iodide (164, 167), was first found occurring naturally by Power and Salway (88) (see Table 1). The alkaloid *methylecytisine* (*N*-methylcytisine, caulophylline) has been characterized by the following derivatives: picrate, m.p. 234° (32); picrolonate, 224–225° (83); hydriodide, 246° (83); methiodide, 276.5° (83); perchlorate, 282° (7); aurichloride, 207° (83); platinichloride, 290° (83). There are two asymmetric carbons in the cytisine (or *N*-methylecytisine) structure (LXI), but the *meta*-bridge is necessarily fixed in the *cis*-position so that only one racemic mixture is theoretically possible. The enantiomorph of (–)cytisine has not been found in nature.

a. The Structure of Cytisine. The correct molecular formula for cytisine, $C_{11}H_{14}N_2O$, was assigned by Partheil (168) in 1890, on the basis of analyses of the aurichloride and platinichloride. It was apparent from the behavior of cytisine with methyl iodide (164, 167), and its formation of mononitroso and monoacetyl derivatives (164), that one of the nitrogen atoms was secondary and that the other nitrogen was probably bound in the tertiary form. The alkaloid apparently forms both mono- and di-hydrochlorides (169, 170), but otherwise cytisine is monoacidic. The tertiary nitrogen was thus only feebly basic. The secondary nitrogen is a component of a ring since Partheil (170) obtained trimethylamine after two stages of Hofmann degradation. Oxidation of cytisine with strongly alkaline potassium permanganate furnished ammonia, identified by analysis of its platinum chloride double salt (167, 170). Another reac-

tion of the secondary NH group, observed by Freund and Friedmann (165), was its conversion to the N—OH group. Cytisine was oxidized

by hydrogen peroxide to oxycytisine, $C_{11}H_{14}N_2O_2$, m.p. 223–226° (dihydrochloride, m.p. 270°; platinichloride, >325°; nitrate, 100°, acetyl derivative, 117°). The conclusion as to the structure of oxycytisine was reached on the basis of its reconversion to cytisine upon sulfur dioxide reduction and its positive reactions with ammoniacal silver nitrate and Fehling's solutions. It was found by Partheil that the oxygen in cytisine was not present as methoxyl, hydroxyl, ketone, or aldehyde.

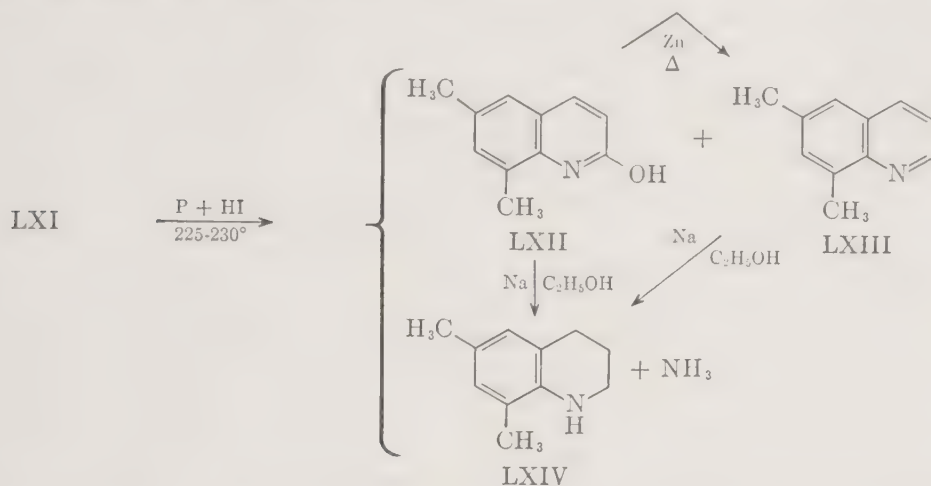
The presence of an aromatic type ring in cytisine was manifest in the substitution reactions of the alkaloid. Partheil (171) observed that cytisine formed a dibromo derivative when treated with bromine in various solvents, of which ethanol was the most satisfactory. The dibromocytisine, $C_{11}H_{12}Br_2N_2O$ (hydrobromide hemihydrate, m.p. 223°; nitrate, 196–197°; acetyl derivative, 164°), resulted from the replacement of two hydrogen atoms by bromine atoms. The dibromocytisine was unchanged on boiling with barium hydroxide or silver hydroxide (171), and Lammers (172) found that reduction of the dibromo compound, m.p. 65–73°, with sodium amalgam and water or with zinc and sulfuric acid regenerated cytisine. Reduction with zinc and acetic acid apparently furnished a monobromocytisine. That the secondary amine function remained intact in dibromocytisine was demonstrated by the preparation of an *N*-acetyl derivative (171), an *N*-methyl derivative (172) (hydrobromide, m.p. 197–198°), and an *N*-nitroso derivative, m.p. 214°, obtained by Freund and Horkheimer (173) through treatment of dibromocytisine hydrobromide with potassium nitrite or treatment of dibromocytisine with nitric acid. Chlorination of cytisine in water solution similarly produced a dichlorocytisine, $C_{11}H_{12}Cl_2N_2O$, isolated as the hydrochloride (172).

Further evidence of aromaticity in the cytisine molecule was obtained from the nitration reaction, Partheil (171) obtaining a product, $C_{11}H_{12}N_4O_4$, m.p. 237° (or 240° (165)). The product, because of its formula, its method of formation, and its positive Liebermann's nitroso reaction, was regarded as a nitronitrosocytisine. Freund and Friedmann (165), in a repetition and extension of Partheil's work, converted the nitronitrosocytisine, $C_{11}H_{12}N_4O_4$, by hydrochloric acid hydrolysis in hot ethanol solution to nitrocytisine, $C_{11}H_{13}N_3O_3$, m.p. 185–188° (hydrochloride, d.p. 270–280°; phenylthiourea, m.p. 252–253°; acetyl derivative, m.p. 223–225°). Such behavior is typical of a nitrosamine, and the nitronitrosocytisine could be regenerated from nitrocytisine hydrochloride by treatment with potassium nitrite. Additional indication of the constitution of nitronitrosocytisine was furnished by the conversion of acetylcytisine to acetylnitrocytisine, m.p. 223–225°, also obtained by acetylation of the hydrolysis product of nitronitrosocytisine. As with halogena-

tion, it was evident that the cytosine molecule offered two positions for aromatic nitration, since a later paper from Freund's laboratory (173) described the isolation of a second nitronitrosocytosine from the reaction of cytosine with nitric acid. The β -nitronitrosocytosine, m.p. 275° , was hydrolyzed to β -nitrocytosine, m.p. 203° (hydrochloride, m.p. 293°), which was reconvertible to the same nitronitrosocytosine with nitrous acid. The isomeric nitrocytosines could be accounted for on the basis of two different replaceable hydrogens in the aromatic portion of cytosine. The monosubstituted compounds were capable of further substitution. α -Nitrocytosine, m.p. $185-188^{\circ}$ (see above), was brominated to give α -nitrobromocytosine, $C_{11}H_{12}BrN_3O_3$, m.p. 135° (hydrobromide, m.p. 286° ; hydrochloride, $>290^{\circ}$; nitrate, 238° ; *N*-nitroso derivative, 245°) (173). Conclusive evidence that the nitro group in nitrocytosine and in the related compounds was attached to an aromatic nucleus was provided in a study of the properties of the derived aminocytosine (165). The dihydrochloride (d.p. 305°) of aminocytosine, $C_{11}H_{15}N_3O$, was obtained by tin and hydrochloric acid reduction of nitronitrosocytosine. The process involved the splitting of the nitrosamine and the reduction of the nitro group. The primary amino group in the product proved to be aromatic, since aminocytosine underwent normal diazotization and coupling. Acetylnitrocytosine was similarly reduced to acetylaminocytosine, $C_{13}H_{17}N_3O_2$, m.p. $242-245^{\circ}$, which could be hydrolyzed to aminocytosine and in turn diazotized and coupled with R-acid to give a dark red dye.

It was thus established that cytosine contained a secondary nitrogen, a tertiary nitrogen, an inert oxygen, and an aromatic ring with two easily replaceable hydrogens. The type of aromatic ring present was but vaguely indicated by the early work of Buchka and Magalhaes (169), who observed that distillation of cytosine with soda-lime gave an oil exhibiting positive pyrrole tests, and Partheil (170), who observed that distillation of cytosine with sodium hydroxide gave a pyridine derivative. The most illuminating information concerning the nature of the ring system in cytosine was obtained from the degradation of the alkaloid with phosphorus and hydrogen iodide. Yet this information was misleading until it finally received the correct interpretation. It will be best to assume the correct structures of the degradation products and then to retrace the logic which has established them. Freund and Friedmann (165) corroborated Lammer's finding (172) of the lack of reaction of hydrogen iodide with cytosine at raised temperature, but found that red phosphorus and hydrogen iodide in a sealed tube at 225° converted cytosine to $C_{11}H_{11}NO$, a weak base which was unchanged on heating with potassium hydroxide and which appeared to undergo nitra-

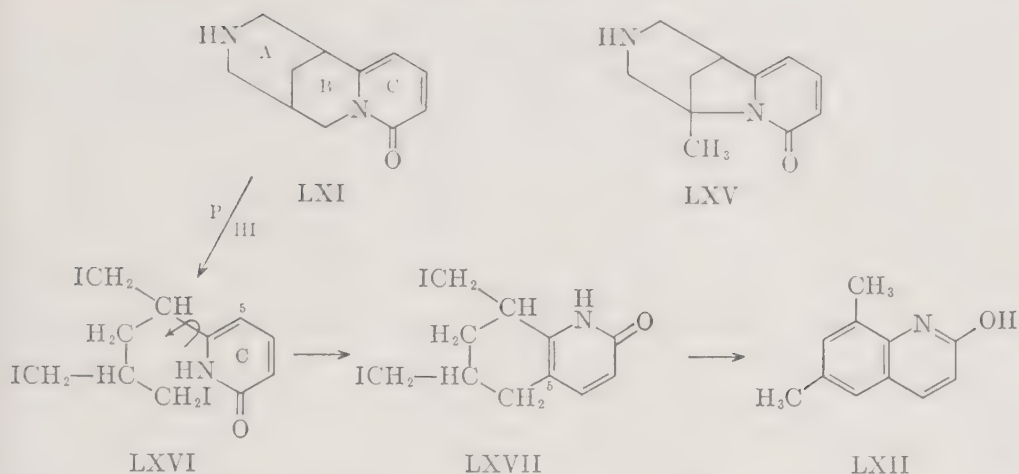
tion when treated with nitric acid. This product (LXII), m.p. 199°, was called "cytisine" by Freund (174), who also isolated from this reaction ammonia and a stronger base, called " β -cytisolidine" and characterized by its platinichloride (m.p. 235°) and picrate (m.p. 228–229°). Freund's original molecular formula for β -cytisolidine was modified by Ewins (175) to $C_{11}H_{11}N$ (LXIII) (nitro derivative, m.p. 104–105°), and it was Ewins who isolated the " α -cytisolidine" (LXIV) (platinichloride, m.p. 216°).



of Freund (174), as yet another product of the phosphorus and hydrogen iodide reaction. The interconversions of these three organic bases provided some clues as to their structural formulas. Sodium and ethanol converted both cytosoline (LXII) (174, 175) and β -cytisolidine (LXIII) (175) to α -cytisolidine, $C_{11}H_{15}N$ (LXIV). Zinc dust distillation of cytosoline gave β -cytisolidine. The aromatic nature of cytosoline was indicated by its reduction, by the formation of nitrocytosoline, m.p. 275° , and by its chromic anhydride oxidation to cytosolinic acid, $C_{11}H_9NO_3$, m.p. $>350^\circ$. The oxidation reaction corresponded to the transformation of a methyl group to a carboxylic acid group (174). Treatment of nitronitrosocytisine under the same conditions gave no acid (176). Ewins (175), in repeating the phosphorus and hydrogen iodide reaction of Freund and his collaborators, noticed that α -cytisolidine (LXIV), when dissolved in sulfuric acid and treated with a drop of nitric acid, gave a carmine-red color shading to blue at the edge of the liquid—a color reaction typical of a tetrahydroquinoline. Freund had considered that α -cytisolidine might be 1,8-dimethyl-1,2,3,4-tetrahydroquinoline, but a synthesis (177) of this compound indicated non-identity. Since analysis indicated the absence of a methyl group attached to the nitrogen, Ewins reasoned that α -cytisolidine was a dimethyltetrahydroquinoline in which both methyls were attached to carbon atoms, and that β -cytisoli-

dine was the corresponding parent dimethylquinoline. The synthesis of a number of dimethylquinolines was projected, and 6,8-dimethylquinoline (LXIII), prepared by an unequivocal method, was found to be identical with β -cytisolidine. Derivatives had identical properties (picrate, m.p. 224–225°; platinichloride, 234–235°; hydrochloride, 246°; nitro derivative, 104–105°) and melting points of mixtures in all cases showed no depression. 6,8-Dimethylquinoline (LXIII) was reduced to 6,8-dimethyl-1,2,3,4-tetrahydroquinoline (LXIV) by means of sodium and ethanol (175), and this product was found to be identical with α -cytisolidine. Derivatives (picrate, m.p. 147–148°; platinichloride, 214–215°; *N*-methyl hydriodide, 166°; *N*-benzoyl, 103°) of authentic LXIV and α -cytisolidine had identical melting points. This synthetic comparison also established the constitution of cytisoline, $C_{11}H_{11}NO$, as a hydroxydimethylquinoline. Ewins observed that the compound gave the brown-red color with ferric chloride characteristic of a hydroxyquinoline, but he did not establish the position of the hydroxyl group. This was accomplished by Späth (178), who synthesized 2-hydroxy-6,8-dimethylquinoline (LXII) and found it to be identical with cytisoline, after having observed (179) that cytisoline gave color reactions similar to carbostyryl and possessed one active hydrogen as indicated in a Zerewitinoff determination. Derivatives of 2-hydroxy-6,8-dimethylquinoline and cytisoline (2-chloro, 2-methoxy, reduction product with sodium and ethanol, oxidation product with chromic acid, nitration product) were identical. With the structure of the phosphorus and hydrogen iodide degradation products of cytisine established as quinoline derivatives (LXII, LXIII, LXIV), it was necessary to decide if the quinoline ring system existed preformed in the alkaloid.

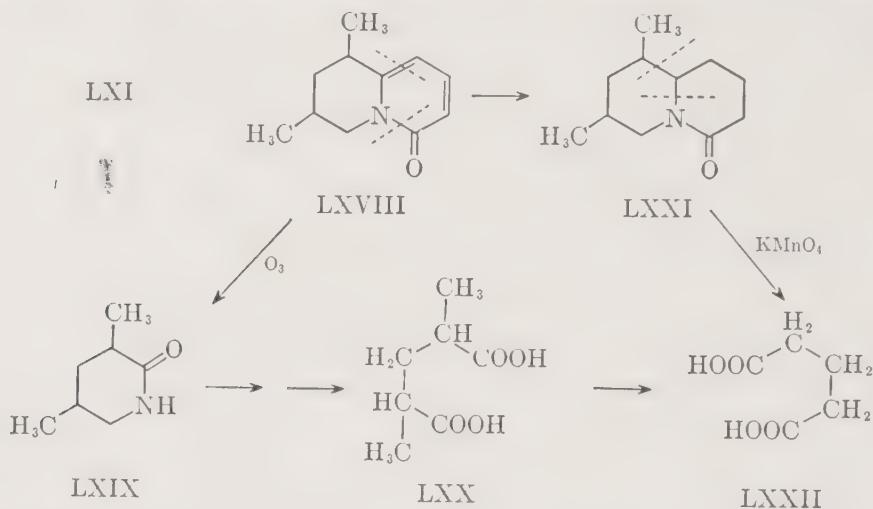
Späth (178) believed that the quinoline ring system was present in cytisine, although he observed that no migration of the *N*-methyl group took place when model compounds, 1,8-dimethyl-2-quinolone and 1,6-dimethyl-2-quinolone, were heated with phosphorus and hydrogen iodide. He also observed that cytisine and 1-methyl-2-pyridone gave identical van de Moer's color reactions. Ing (180) marshalled the evidence for the presence of an α -pyridone ring in cytisine and concluded that the production of the quinoline compounds during phosphorus and hydrogen iodide treatment of cytisine involved some intramolecular change. Ing suggested on this basis two possible formulas for cytisine, LXI and LXV, of which the former has been proved correct although he originally favored the latter (180). The conversion of the α -pyridone compound (LXI) to a quinoline derivative (LXII) could then be visualized in the following manner. The effect of the phosphorus and hydriodic acid would be to remove the imino group as ammonia and to break the



carbon linkage to the pyridone nitrogen with the formation of LXVI. The equivalent two of the three CH_2I — groups in LXVI are in a position favorable for attack on the activated 5-position of the pyridone nucleus, and such attack would lead to the rearranged α -pyridone LXVII, which would be expected to undergo dehydriodination and isomerization readily to yield the fully aromatic 2-hydroxy-6,8-dimethylquinoline (LXII). The formation of the other quinoline products (LXIII, LXIV) from this would follow logically.

The Hofmann exhaustive methylation of cytisine, which had been investigated originally by Partheil (170), was finally useful in adding evidence that cytisine was best represented by LXI. Ing (180), in a repetition of Partheil's methylation procedure, discovered that *des-N*-dimethylcytisine methohydroxide could be decomposed in boiling amyl alcohol to trimethylamine and a crystalline product, m.p. 300° , of dimeric structure, $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_2$. The dimerization was considered to be evidence of the lack of a hydrogen atom on one of the carbon atoms *beta* to the secondary nitrogen, and therefore to favor LXV as the structure of cytisine (180). Späth and Galinovsky (181) showed, however, that polymerization could be avoided by the technique of following each degradation step with hydrogenation. Thus, methylcytisine methohydroxide lost water on heating in vacuum at 90° to yield *des-N*-dimethylcytisine, which absorbed one mole of hydrogen on catalytic reduction to give dihydro-*des-N*-dimethylcytisine, $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}$ (picrate, m.p. 174 – 175° , $[\alpha]_D^{24} - 46.9^\circ$ (methanol)), which still possessed optical activity. The second Hofmann degradation step, on the hydrogenated material, proceeded smoothly to give trimethylamine and an unsaturated base, $\text{C}_{11}\text{H}_{13}\text{NO}$, called "dihydrohemicytisylenes," which possessed almost no optical activity. Controlled hydrogenation of this compound over palladium on charcoal produced "tetrahydrohemicytisylenes," $\text{C}_{11}\text{H}_{15}\text{NO}$

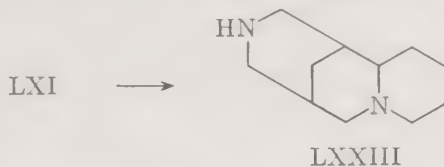
(formed a crystalline platinichloride and gave color reactions of an α -pyridone). No carbon atom was lost from the cytosine moiety in the process, nor was any other abnormality observed. The development of unsaturation at each degradation stage indicated the presence of hydrogen on both of the carbons *beta* to the secondary nitrogen atom, consistent with formula LXI for cytosine (and consistent with other formulas suggested as possibilities by Späth and Galinovsky). A Herzig-Meyer determination indicated the absence of an N—CH₃ group in tetrahydrohemicytisylene (just as in cytosine) and therefore showed that the remaining nitrogen atom was common to two rings. Further reactions of tetrahydrohemicytisylene are indicated employing the structural formula (LXVIII) established as correct for this molecule. Ozonization of tetrahydrohemicytisylene (LXVIII) furnished a lactam (LXIX), C₇H₁₃NO,



m.p. 70–75°, which was converted by hydrochloric acid hydrolysis, followed by potassium permanganate oxidation, to a mixture of *meso*- and *dl*-forms of $\alpha\alpha'$ -dimethylglutaric acid (LXX), identified as such (181). When catalytic reduction of tetrahydrohemicytisylene to octahydrohemicytisylene (LXXI) was followed by permanganate oxidation, glutaric acid (LXXII) was produced, identified by comparison of the dianilide with an authentic sample, m.p. 225°. From these “pieces” of the molecule, structure LXVIII was derivable for tetrahydrohemicytisylene (181), based on Ing’s formula LXI for cytosine. Cytosine itself could be converted to a tetrahydrocytosine, C₁₁H₁₈N₂O, m.p. 113–114°, which on permanganate oxidation gave oxalic acid and the same glutaric acid (m.p. 96–97°) portion obtained on similar treatment of tetrahydrohemicytisylene.

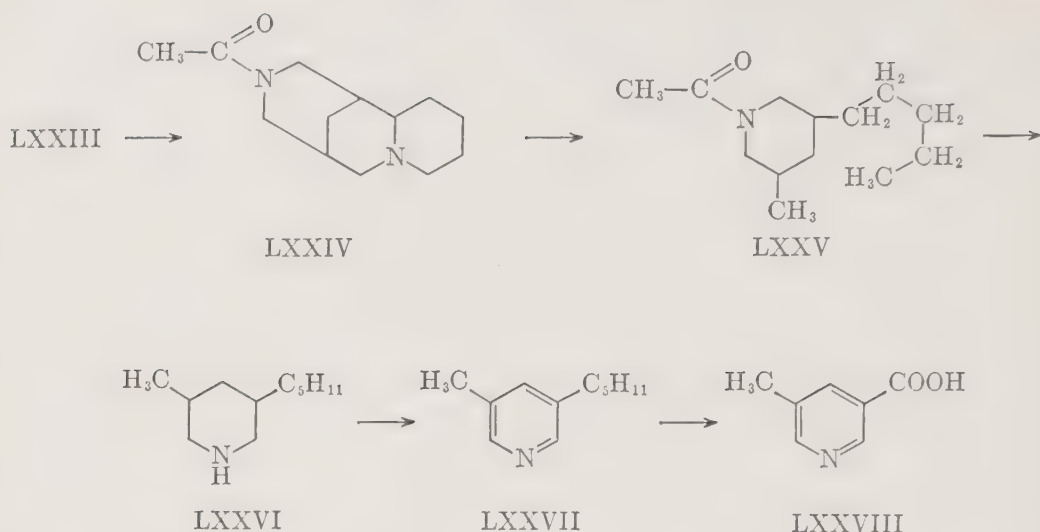
The modified Hofmann exhaustive methylation of another reduction product of cytosine was useful in confirming the tertiary and bridge-head

character of the second nitrogen in the alkaloid (the "first" nitrogen is that of the secondary amino group). "Tetrahydrodesoxycytisine" (LXXIII) was first prepared from cytisine by Freund and Horkheimer



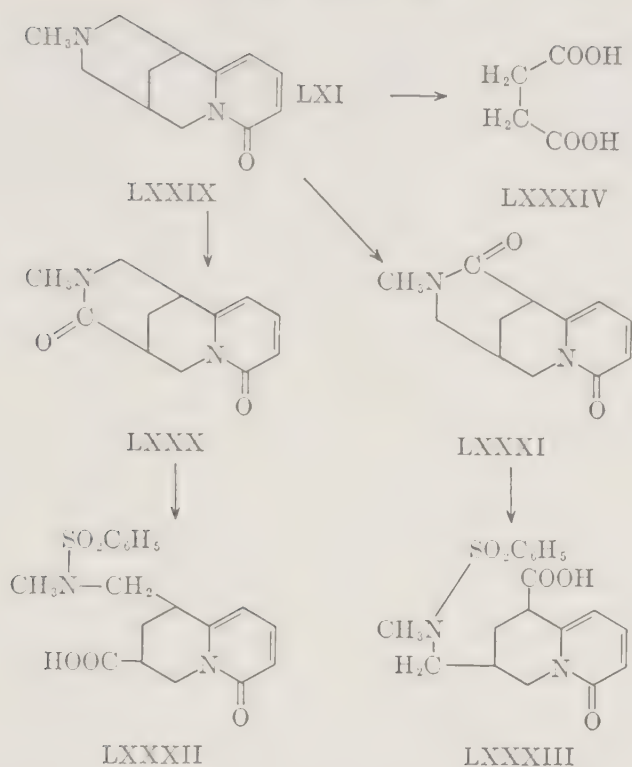
(173) by electrolytic reduction in sulfuric acid at a lead cathode. The product, $C_{10}H_{20}N_2$, was fully characterized by these workers (dihydrochloride, m.p. 282° ; platinichloride, 235° ; *N*-nitroso, 150° ; phenylthiourea, 108° ; *N*-methyl hydriodide, $205\text{--}206^\circ$; *N*-methyl methiodide, 283°) and they carried out a normal Hofmann degradation in which trimethylamine was lost at the second stage, thus indicating that only the secondary nitrogen was involved. The Hofmann exhaustive methylation of LXXIII (see also 188) was modified by Späth and Galinovsky (181) by hydrogenation following each degradation step. Thus, *des-N*-dimethyltetrahydrodesoxycytisine, the first stage product, was catalytically hydrogenated to dihydro-*des-N*-dimethyltetrahydrodesoxycytisine, $C_{13}H_{26}N_2$, b.p. 132° (11 mm.). The crystalline dimethiodide of the latter, d.p. $325\text{--}327^\circ$, was converted in the usual manner to trimethylamine and a base which absorbed two moles of hydrogen catalytically to give $C_{12}H_{25}N$. This step therefore included loss of the secondary nitrogen and opening of the ring-system containing the tertiary nitrogen. The $C_{12}H_{25}N$ base contained one *N*-methyl group and was degraded, followed by hydrogenation, to a base $C_{13}H_{29}N$, which possessed two *N*-methyl groups. These facts are consistent with the structures assigned to tetrahydrodesoxycytisine (LXXIII) and cytisine (LXI).

It was found possible to remove the tertiary nitrogen and leave the secondary nitrogen by applying the modified Hofmann exhaustive methylation to *N*-acetyltetrahydrodesoxycytisine (m.p. $70\text{--}71^\circ$). By operating on this compound (LXXIV), Späth and Galinovsky (182) were able to establish conclusively the fact that ring A of cytisine (see LXI) was piperidine rather than a methylpyrrolidine, and thus to rule out of consideration any suggested formula (181) containing a five-membered ring A. The experimental method was as follows. The methiodide (m.p. $249\text{--}250^\circ$) of *N*-acetyltetrahydrodesoxycytisine (LXXIV) was converted to the quaternary base and this was subjected to the Hofmann degradation. The resulting *des*-base was catalytically hydrogenated. The process was repeated, and at the third stage the original tertiary nitrogen was eliminated as trimethylamine. The other product, $C_{13}H_{23}NO$, was hydrogenated and the acetyl group was removed by hydro-



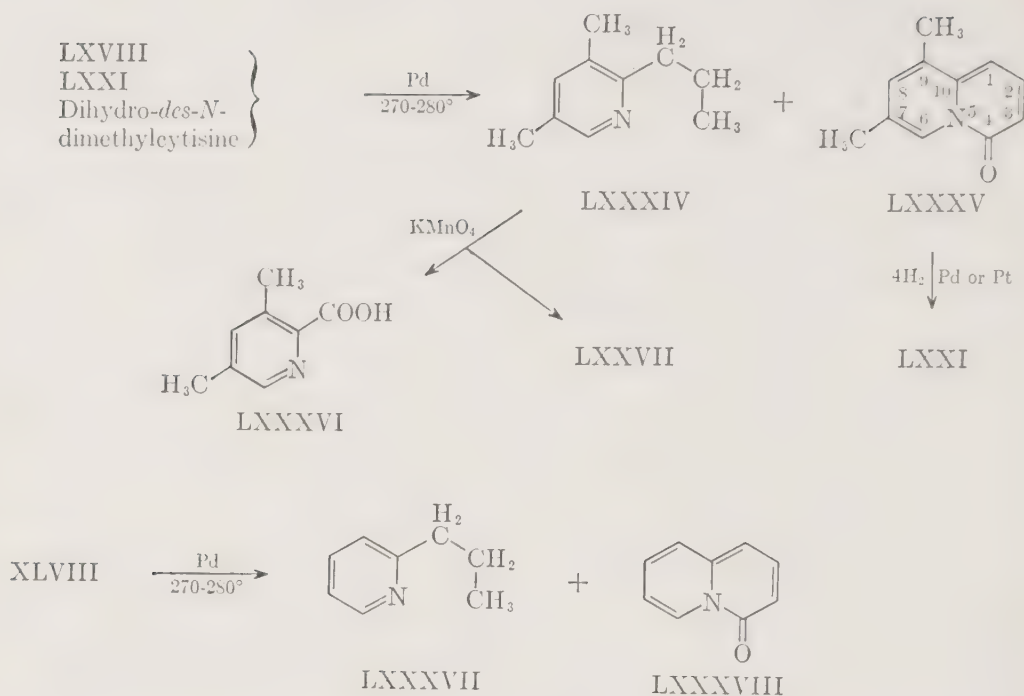
chloric acid treatment. The base obtained was dehydrogenated over palladium at 180° , with the production of a pyridine base, $C_{11}H_{17}N$ (picrate, m.p. 145°). The substituted pyridine was oxidized by permanganate to β -methylnicotinic acid (LXXVIII), m.p. $214\text{--}215^\circ$. Also obtained was a small quantity of a high-melting (*ca.* 300°) compound, which was probably dinicotinic acid since it was converted to nicotinic acid after melting with decomposition. The facile production of the pyridine base, $C_{11}H_{17}N$, was ample evidence for the piperidine moiety of ring A. The loss of four carbons with concomitant formation of one carboxylic acid group was evidence for an amyl side-chain in the substituted pyridine, and on the basis of previous knowledge concerning cytosine, the compound could be assigned the structure 3-methyl-5-*n*-amylpyridine (LXXVII). Its piperidine precursor would then be 3-methyl-5-*n*-amylpiperidine (LXXVI) and the acetyl derivative, LXXV.

Oxidation experiments also served to provide conclusive evidence for the structure of cytosine as represented (LXI). Mild oxidation of methylcytosine (LXXIX), $C_{12}H_{16}N_2O$, with barium permanganate, carried out by Ing (183), gave a mixture of isomeric lactams, $C_{12}H_{14}N_2O_2$. These were designated as *N*-methyl- α -cytisamide, m.p. $214\text{--}215^\circ$, and *N*-methyl- β -cytisamide, m.p. $179\text{--}180^\circ$, and were separated by differential solubility in ethyl acetate. Each was hydrolyzed by alkali to the corresponding cytisamic acid, and the amino acids were characterized as their benzenesulfonyl derivatives, $C_{18}H_{20}N_2O_5S$: *N*-benzenesulfonyl-*N*-methyl- α -cytisamic acid, m.p. $152\text{--}153^\circ$, and *N*-benzenesulfonyl-*N*-methyl- β -cytisamic acid, m.p. $130\text{--}131^\circ$. Formula LXI for cytosine and LXXIX for methylcytosine would give rise to two structurally isomeric lactams, LXXX and LXXXI, and two structurally isomeric acids,



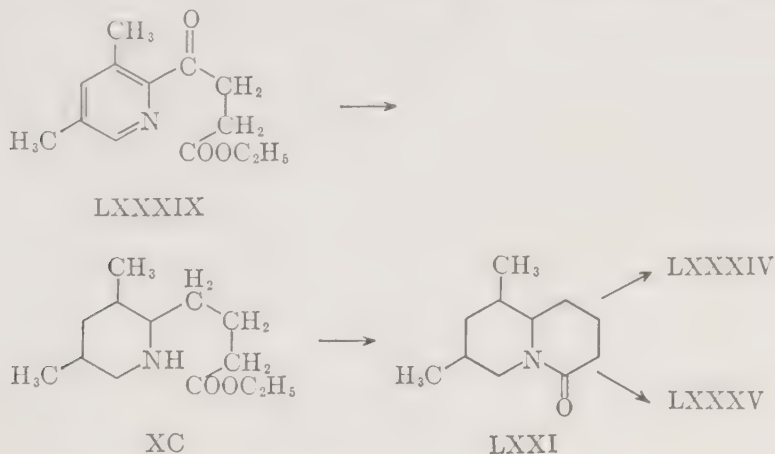
LXXXII and LXXXIII. One of these acids, LXXXIII, would be a substituted pyridine-2-acetic acid, a type which is known to undergo decarboxylation readily (184). Ing found that the β -acid lost the theoretical amount of carbon dioxide at the melting point to give a residual benzenesulfonyl-base, $C_{17}H_{20}N_2O_3S$, m.p. 141–142°. The β -series could therefore be represented as LXXXI and LXXXIII and the α -series as LXXX and LXXXII. Strong oxidation of cytisine according to the procedure of Späth and Galinovskiy (182) resulted finally in the isolation and identification of a small quantity of succinic acid (LXXXIV), which could theoretically arise from the carbons of rings A and B of LXI if decarboxylation is also assumed to occur.

Dehydrogenation experiments provided further support for formula LXI for cytisine. When the alkaloid was subjected to dehydrogenation over palladium, a rearranged product, 2-hydroxy-6-methylquinoline, was obtained (185, 186), reminiscent of the quinolizidine-to-quinoline rearrangement observed under phosphorus and hydrogen iodide treatment. Dehydrogenation of tetrahydrohemicytisylene (LXVIII) (186) was more instructive. The products obtained on heating LXVIII over palladium were a liquid, $C_{10}H_{15}N$, and a solid, $C_{11}H_{11}NO$. The same products were also obtained on dehydrogenation of octahydrohemicytisylene (LXXI) and dihydro-*des-N*-dimethylcytisine (see page 149), and when the latter



was employed dimethylamine was a third product. The structure of the liquid product, $\text{C}_{10}\text{H}_{15}\text{N}$, which appeared to be a pyridine base (picrate, m.p. $150-151^\circ$; methiodide, m.p. $127-128^\circ$), was indicated as 3,5-dimethyl-2-propylpyridine (LXXXIV) on the basis of its permanganate oxidation products: β -methylnicotinic acid (LXXXVII), m.p. $214-215^\circ$, and 3,5-dimethylpicolinic acid (LXXXVI), m.p. $152-153^\circ$. The solid dehydrogenation product, $\text{C}_{11}\text{H}_{11}\text{NO}$, m.p. 83° (picrate, m.p. $149-150^\circ$; hemihydrate, m.p. $64-65^\circ$), had four less hydrogens than tetrahydrohemicytisylen, was only slightly basic, and exhibited color reactions and fluorescence characteristic of a conjugated α -pyridone. It absorbed four moles of hydrogen on catalytic reduction to give $\text{C}_{11}\text{H}_{19}\text{NO}$, similar to octahydrohemicytisylen (LXXI). Späth and Galinovsky (186) suggested that the solid product should be represented as LXXXV, 4-keto-7,9-dimethylquinolizine, and supported their argument with similar dehydrogenation experiments on the model compound 4-ketoquinolizidine (XLVIII) (133). The products of palladium dehydrogenation of 4-ketoquinolizidine were 2-propylpyridine, $\text{C}_8\text{H}_{11}\text{N}$ (LXXXVII), identified as the picrate (m.p. 70°) and the oxidation product, picolinic acid (m.p. $136-137^\circ$), and 4-ketoquinolizine, $\text{C}_9\text{H}_7\text{NO}$ (LXXXVIII), m.p. $72-73^\circ$ (picrate, m.p. $136-137^\circ$). The 4-ketoquinolizine (LXXXVIII) had properties very similar to those of the solid dehydrogenation product, $\text{C}_{11}\text{H}_{11}\text{NO}$, from tetrahydrohemicytisylen. The closely parallel behavior of the model compounds with those of alkaloid origin

constituted strong corroborative argument for the structures assigned. For final identification of LXXXIV and LXXXV, these compounds were synthesized by Späth and Galinovsky (187) from non-alkaloid starting



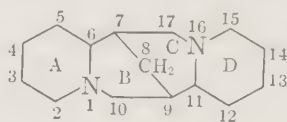
materials. Ethyl β-(3,5-dimethyl-2-pyridoyl)propionate (LXXXIX), prepared by condensation of ethyl 3,5-dimethylpicolinate with diethyl succinate in the presence of sodium ethoxide, was subjected to Clemmensen reduction followed by catalytic hydrogenation to give XC. Thermal cyclization of XC gave a compound LXXI, $C_{11}H_{19}NO$, resembling octahydrohemicytisine, which underwent dehydrogenation over palladium in a similar manner. The products, LXXXIV and LXXXV, were identical with those obtained from the alkaloidal source-material. Authentic 3,5-dimethyl-2-propylpyridine (LXXXIV) was prepared by an additional, unequivocal method (187) for direct comparison purposes.

b. Synthetic Experiments with Cytisine. There has been interest in the total synthesis of the alkaloid cytisine, but the attempts which have been reported have not been successful (189, 190, 191, 192). With the purpose of investigating possible partial synthesis of anagryne (see below), Litterscheid (193) made various *N*-butyl derivatives of cytisine. Without knowledge of the correct structure of either alkaloid, this work in 1900 nevertheless came very close to the mark, since cytisine and anagryne are closely related. Other *N*-substituted derivatives of cytisine have been made during the course of investigations on this alkaloid, for example, the phenylthiourea, m.p. 254° (194), and the *p*-toluenesulfonyl (m.p. $204\text{--}205^{\circ}$) and 1-naphthalenesulfonyl (m.p. $229\text{--}230^{\circ}$) derivatives (195). Cytisine has also been used as a starting material for the synthesis of derivatives which, it was hoped, would not possess the nicotine like toxicity of cytisine (196) and *N*-methyleytisine (197). Ing and Patel (198) obtained *N*-β-hydroxyethyleytisine by reaction of ethylene oxide with cytisine and made the benzoic and cinnamic

esters of this amino alcohol. Esters of *N*- γ -hydroxypropylcytisine were obtained by the condensation of the appropriate γ -chloropropyl ester with cytisine: benzoate, cinnamate, phenylcarbamate, α -naphthylcarbamate, *p*-aminobenzoate. All esters were isolated as their hydrobromides. All except the *p*-aminobenzoate ester were found to have pronounced local anesthetic action and all except the phenylcarbamate were less toxic than cocaine (199). Their pharmacological behavior did not resemble that of nicotine.

3. SPARTEINE, $C_{15}H_{26}N_2$

Sparteine (XCI), $C_{15}H_{26}N_2$, has been found in nature in both *d*- and *l*-forms and also as a mixture (racemic plus excess *l*-). *l*-Sparteine



XCI

(lupinidine), the more common form, was first isolated by Stenhouse (200) in 1851. Methods for qualitative and quantitative estimation of this alkaloid in plants have been developed, and Jaretzky and Axer (201) have indicated the presence of *l*-sparteine in a large number of genera and species which have not been included in Table 1. Derivatives which are useful for characterization and identification of the alkaloid are: methiodide, m.p. 239–240° (44); dihydriodide, 257–258° (77); dihydrobromide, 194–195° (65); dipicrate, 208° (203); trinitro-*m*-cresolate, 218° (102); sulfate, 268° (63); monoperchlorate, 172° (63); platinichloride, 248° (44); zinc chloride, 325° (65); mercurichloride, 200° (65). *d*-Sparteine (pachycarpine, hexahydrodesoxyanagryne) has been characterized through the formation of similar salts: methiodide, m.p. 236–238° (81); methiodide 223–224° (81); dihydriodide, 255–257° (81); monohydriodide, 235–236° (81); dipicrate, 208.5° (19); monoperchlorate, 172–173° (19); platinichloride, 261° (32); aurichloride, 192–193° (81).

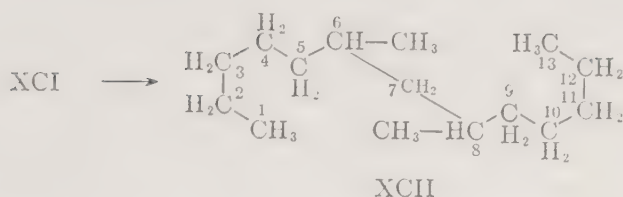
a. The Structure of Sparteine. The correct formula, $C_{15}H_{26}N_2$, was assigned by Stenhouse (200) at the outset of work on this alkaloid and was corroborated by Mills (202) by analysis of the carefully dried liquid itself. The presence of both nitrogens in tertiary amino linkage was indicated by the work of Moureu and Valeur (203), who showed that both nitrogens could be titrated, that sparteine formed neutral and acid salts (see also 77), that it did not react with nitrous acid and formed a methiodide (205). The saturated nature of the molecule was indicated by the lack of reaction with permanganate or reducing agent (204, 206) and the ring structure was indicated by the molecular formula and the lack of

any *N*-methyl group. Willstätter and Marx (207) confirmed the findings of Moureu and Valeur and suggested that the sparteine molecule probably possessed four rings, judging from its formula and its saturated character. As pointed out by Wackernagel and Wolffenstein (208), the earlier findings of Ahrens (209, 210) that the molecule was unsaturated were apparently in error.

Comparatively little structural information was gleaned from oxidation experiments on sparteine although some of the products were useful in the final determination of structure. A product called "oxysparteine" (the name would be more indicative if it were "oxosparteine"), $C_{14}H_{24}N_2O$, m.p. 84° (or 87° (188)), was obtained by mild oxidation by Ahrens (211, 212, 213). The most satisfactory reagent proved to be alkaline ferricyanide (214), and the product was characterized through the formation of a number of salts—all of them monoacidic (hydrochloride monohydrate, m.p. $>230^\circ$; nitrate monohydrate, 207° ; methiodide, 191 – 193° ; platinichloride, 228 – 229° ; aurichloride, 190 – 191°). Oxysparteine appeared to be a lactam even though it was resistant to hydrolysis, since it contained one inert nitrogen and an inert oxygen. Ahrens (209) obtained a different oxidation product, $C_{15}H_{26}N_2O_2$, m.p. 128 – 129° , on treatment of sparteine with hydrogen peroxide (hydrobromide, m.p. 146 – 147° ; hydriodide, 137° ; mercurichloride, 193°) (212), and Wackernagel and Wolffenstein (208) showed that this was probably the amine oxide, with oxygen on both of the nitrogens. Sparteine was readily regenerated from this "sparteine *N,N'*-dioxide" by treatment with sulfurous acid or zinc and hydrochloric acid. Oxysparteine was also found to form a dioxide, $C_{15}H_{24}N_2O_3$, on further oxidation with hydrogen peroxide (platinichloride, d.p. 200° ; aurichloride, m.p. 136 – 137°). Strong permanganate oxidation of sparteine was found by Germain (215) to give succinic acid.

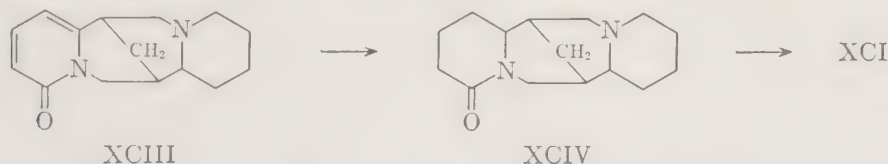
Much work was done, especially by Moureu and Valeur, on the Hofmann exhaustive methylation of sparteine. To begin with, two different monomethiodides of sparteine were obtained (216, 249, 250): " α ," m.p. 240° , $[\alpha]_D - 22.75^\circ$ (hydriodide, -17.1°), and " α' ," $[\alpha]_D - 47.2^\circ$ (hydriodide, -40.3°), and it was concluded (217) that these were stereoisomers rather than structural isomers (*cf.* 128, 217), a conclusion supported by later work. Moureu and Valeur followed a study of the isomeric diethiodides (218, 223, 224, 225, 249) and the methiodide hydriodides (219, 222, 228) with a lengthy study on the Hofmann degradation (226, 227, 229–248). The alkaloid was completely freed from nitrogen after five iodomethylation stages, or actually six since one of the methylations (number three) was double: sparteine \rightarrow methylsparteine \rightarrow dimethylsparteine \rightarrow trimethylamine + methylhemisparteilene \rightarrow

dimethylsparteilene \rightarrow trimethylamine + sparteilene (according to the nomenclature of Moureu and Valeur). Methylhemisparteilene was optically active and dimethylhemisparteilene and sparteilene were inactive. Sparteilene, $C_{15}H_{20}$, b.p. $157-159^\circ$ (18 mm.), behaved as expected of a hydrocarbon with six double bonds and furnished formic acid when oxidized with permanganate. The conclusions reached after these many experiments were that both nitrogen atoms were at the bridge-head of a bicyclic structure and that the molecule as a whole was symmetrically constituted (251). Some sixteen years later, Schöpf and Braun (252) repeated the first Hofmann degradation step of Moureu and Valeur and carried out characterization experiments on the α -des-N-methylsparteine, $C_{16}H_{28}N_2$ (b.p. $173.5-174^\circ$ (10 mm.), m.p. $30-31^\circ$, $[\alpha]_D - 55.4^\circ$; dihydriodide, m.p. $236-237^\circ$), thus obtained. For example, hydrogenation over platinum gave dihydro- α -des-N-methylsparteine, $C_{16}H_{30}N_2$ (m.p. 64° ; dihydriodide, m.p. $267-268^\circ$), bromination gave dibromo- α -des-N-methylsparteine, $C_{16}H_{28}Br_2N_2$ (perchlorate, m.p. 267°), and permanganate oxidation gave a glycol, $C_{16}H_{30}N_2O_2$ (m.p. 200° ; gives an amino acid with potassium chlorate and osmium tetroxide). Clemo and Raper (126) likewise repeated the first stage of the Hofmann degradation of sparteine and carried the degradation of oxysparteine to the second stage. A plan to follow, with sparteine, each degradation step by hydrogenation, which method had been so successful with the alkaloid lupinine (119), was projected by Winterfeld (235) in 1928, but carried out successfully and reported by Karrer and his coworkers (254) in 1930. Karrer, Shibata, Wettstein, and Jacobowicz (254) obtained, after six stepwise degradations followed by catalytic hydrogenations, a pentadecane, $C_{15}H_{32}$, b.p. 242° (729 mm.) of unknown constitution. This would correspond to the completely hydrogenated product from Moureu and Valeur's sparteilene, $C_{15}H_{20}$. The compound $C_{15}H_{32}$ was characterized as completely as possible for a saturated hydrocarbon and was compared with synthetic 4-methyl-6-propylundecane, 6-propyldodecane, and 6-methyl-7-ethyldodecane. One of these products would have resulted from the modified Hofmann degradation if any of the formulas postulated by Karrer and his coworkers (119, 254) had been correct. However, it was considered impossible to decide among these three possibilities since the physical properties of all four pentadecanes were so similar. It was not until after the structure of sparteine was considered fully established that 6,8-dimethyltridecane (XCII) was synthesized by Schirm and Besendorf (255) and found to agree in all its physical properties with the $C_{15}H_{32}$ from the alkaloid. The synthesis of XCII was achieved by condensation of 2-iodoheptane with sodio acetoacetic ester, followed by ketonic split, amylmagnesium iodide



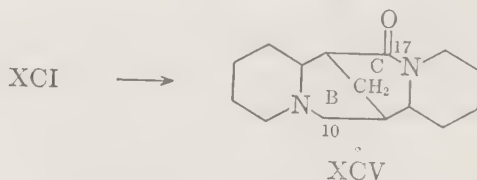
treatment, heating with potassium acid sulfate, and finally hydrogenation. It was also after the structure of sparteine had been satisfactorily established that Späth and Galinovsky (256) carried out the modified Hofmann degradation on oxysparteine to the stage of trimethylamine elimination and production of "hexahydrohemioxysparteilene," $\text{C}_{15}\text{H}_{27}\text{NO}$. The lactam thus produced should be 1-methyl-3-*n*-amyl-4-ketoquinolizidine. Degradations of sparteine and its derivatives with cyanogen bromide were not fruitful (126, 257).

The correct structure (XCI) of sparteine was proposed by Clemo and Raper (258) after consultation with Ing (6), who had indicated preference for a formula similar to XCI, but with ring D a methylpyrrolidine rather than a piperidine. The main evidence in support of the five-membered ring D was that zinc dust distillation products of sparteine and the related C_{15} lupin alkaloids gave pyrrole-like color reactions. This argument was dispatched by Clemo and Raper, when they showed that cytisine, known to contain only six-membered rings, behaved similarly. The assignment of structure XCI to sparteine was dependent upon the relation of this alkaloid to two other C_{15} lupin alkaloids, anagryne, $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}$ (XCIII), and lupanine $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}$ (XCIV). The close relation of anagryne to cytisine was established by Ing (6), who also found that the catalytic



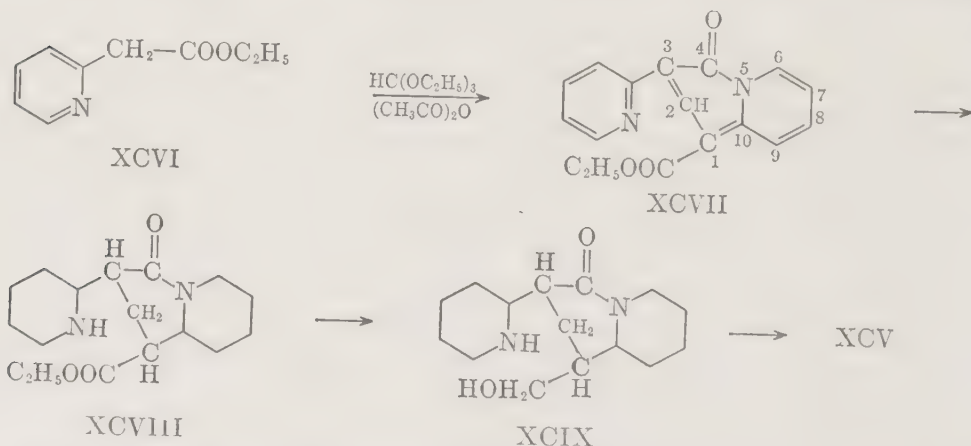
hydrogenation product of anagryne, tetrahydroanagryne, $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}$, was identical with *l*-lupanine, and that the electrolytic reduction product, hexahydrodeoxyanagryne, $\text{C}_{15}\text{H}_{26}\text{N}_2$, was identical with *d*-sparteine. The relation between lupanine (XCIV) and sparteine (XCI) had been established earlier by Clemo, Raper, and Tenniswood (259). *dl*-Lupanine was resolved by means of camphorsulfonic acid. From the *d*-lupanine *d*-camphorsulfonate ($[\alpha]_D$ 45.5°), pure *d*-lupanine ($[\alpha]_D$ 61.4°) was obtained, and from the *l*-lupanine *l*-camphorsulfonate ($[\alpha]_D$ -45.3°), pure *l*-lupanine ($[\alpha]_D$ -61.0°) was obtained. The $\text{C}_{15}\text{H}_{26}\text{N}_2$ base obtained by reducing *d*-lupanine with red phosphorus and hydrogen iodide in a sealed tube at 220–230° was identical with *l*-sparteine. The

isomeric base obtained by reducing *l*-lupanine under the same drastic conditions was identified as *d*-sparteine. When *dl*-lupanine was reduced with phosphorus and hydrogen iodide, the product was *dl*-sparteine, earlier called "deoxylupanine" by Clemo and Leitch (69) (monopicrate, m.p. 135°; dipicrate, 206–207°; methiodide, 226°). Oxidation of *dl*-sparteine, with potassium ferricyanide gave *dl*-oxysparteine, $C_{15}H_{24}N_2O$, (or "isolupanine" (69)), the racemate of the analogous product from *l*-sparteine oxidation (see page 156). The lactam, *dl*-oxysparteine (m.p. 113°), was isomeric with the *dl*-lupanine and was therefore assigned a structure with the carbonyl group in one of the inner rings (B or C, position 10 or 17). The final assignment of structure XCV, with the carbonyl in ring C at the 17-position, to oxysparteine was decided on the basis of the relation of oxylupanine to oxysparteine (258). Oxysparteine (XCV)



subsequently proved to be a key compound in the synthesis of sparteine.

Oxysparteine was also the intermediate which furnished conclusive proof of the ring structure of all the C_{15} lupin alkaloids. Clemo, Morgan, and Raper in 1936 (260) announced the synthesis, from non-alkaloid starting materials, of a compound with structure XCV and established the identity of this compound with the *dl*-oxysparteine obtained by alkaline ferricyanide oxidation of *dl*-sparteine. The synthesis of *dl*-oxysparteine (XCV) was accomplished as outlined below. The Claisen condensation of ethyl 2-pyridylacetate (XCVI) with ethyl orthoformate



in the presence of acetic anhydride furnished 1-carbethoxy-3-(α -pyridyl)-4-ketoquinolizine (XCVII) (m.p. 126°; picrate, m.p. 216°). Reduction

of the aromatic rings by hydrogen over platinum oxide to 1-carbethoxy-3-(α -piperidyl)-4-ketoquinolizidine (XCVIII) and the subsequent Bouveault reduction of the ester group gave 1-hydroxymethyl-3-(α -piperidyl)-4-ketoquinolizidine (XCIX). Closure of ring B was effected by intramolecular alkylation of the intermediate 1-bromomethyl compound in the presence of anhydrous potassium carbonate in a sealed tube. The product XCV, $C_{15}H_{24}N_2O$, and a number of its derivatives were identical with *dl*-oxysparteine (69) and its corresponding derivatives.

Thus, synthesis and degradation met in oxysparteine (XCV), and the ring structure (XCI) common to the C_{15} lupin alkaloids (sparteine, anagyrene, lupanine, aphylline) was thereby established. Galinovsky and Stern (188) were able to convert *d*-lupanine (XCIV) to *l*-sparteine by hydrogenation over platinum in hydrochloric acid solution—milder conditions than the phosphorus and hydriodic acid treatment of Clemons and his coworkers. Galinovsky and Stern also converted anagyrene (XCIII) to *d*-sparteine by catalytic hydrogenation under the same conditions (cf. 6). Alkaline ferricyanide oxidation of *d*-sparteine produced *d*-oxysparteine, m.p. 87° , and a mixture of equal parts of *d*-oxysparteine and *l*-oxysparteine melted at 112 – 113° , identical with the *dl*-oxysparteine obtained synthetically (260) and by oxidation (69). Oxysparteine, unlike lupanine and aphylline, could not be reconverted to sparteine by catalytic reduction (188). The alkaloid pachycarpine, investigated by Orekhov and his coworkers, was considered to be the enantiomorph of *l*-sparteine (81), and its identity with *d*-sparteine was established directly in 1934 (26, see also 188). "*d*-Oxypachycarpine," or *d*-oxysparteine, obtained by ferricyanide oxidation of pachycarpine (*d*-sparteine) was hydrolyzed by hydrochloric acid (261) to an amino acid and isolated as its ethyl ester, $C_{17}H_{30}N_2O_2$, which relactamized in sulfuric acid. The ethyl ester of the amino acid formed *N*-nitroso (m.p. 86 – 88°) and *N*-benzoyl (m.p. 121 – 122°) derivatives.

Mention should be made of a number of oxidation products of sparteine which have been obtained during the course of work on this alkaloid. The preparation of oxysparteine and oxysparteine *N,N'*-dioxide has already been described (208). Schöpf and Braun (252) found that it was also possible to obtain oxysparteine *N*-oxide, $C_{15}H_{24}N_2O_2$ (picrate, m.p. 221°), by peroxide oxidation of oxysparteine. The mono-*N*-oxide could be reconverted to oxysparteine by means of sulfurous acid. Another oxidation product of sparteine, which has not been mentioned before, is γ -aminobutyric acid, obtained by Karrer and Widmer (262) by chromic acid-sulfuric acid oxidation of sparteine (and coniine). A number of dehydrogenation products have been obtained from sparteine. In addition to oxysparteine, Willstätter and Marx (263) obtained, on chromic

acid oxidation of sparteine, a compound $C_{15}H_{24}N_2$, which was called "spartyrine" (m.p. 153–154°; $[\alpha]_D^{18} - 25.96^\circ$ (ethanol)). This product contained a double bond, as did the "dehydrosparteine," $C_{15}H_{24}N_2$, of Wolffenstein and Reitmann (264), obtained by hypobromite oxidation of the alkaloid. However, the properties of spartyrine were very different from those of dehydrosparteine: m.p. 172–173°; $[\alpha]_D^{18} - 255^\circ$ (chloroform). This dehydrosparteine was more completely characterized by Winterfeld and Schirm (265, 266) in a repetition of the work (aurichloride, m.p. 181°; platinichloride, 250°; picrate, 181–182°; dihydrochloride, 248°). Winterfeld (253) obtained yet another dehydrosparteine, $C_{15}H_{24}N_2$ ($[\alpha]_D - 142.1^\circ$ (chloroform)), by the action of two moles of mercuric acetate on sparteine. α -Didehydrosparteine (m.p. 106–107°, $[\alpha]_D - 647^\circ$ (benzene); sulfate, m.p. 253°; perchlorate, 257°; picrate, 164°) and β -didehydrosparteine ($[\alpha]_D - 40.5^\circ$ (benzene); reineckate, m.p. 194°), both $C_{15}H_{22}N_2$, were obtained by treating sparteine with four moles of mercuric acetate (253, 267, 268). Also obtained synthetically by Winterfeld and his coworkers were phenyldehydrosparteine (266), 2-anisoylsparteine (269), and 2-alkylsparteines (270).

b. Isomers of Sparteine. The question as to the number of stereoisomers of the sparteine molecule is best answered by considering molecular models. In the sparteine ring system (XCI) there are four asymmetric carbons, C_6 , C_7 , C_9 , and C_{11} , but the configurations of C_7 and C_9 are interdependent since the C_8 methylene bridge can only span the distance between C_7 and C_9 in a *cis* manner. Clearly, all four rings, being six-membered and saturated, can theoretically exist in chair and boat forms, but it must be assumed on the basis of present knowledge that they are readily interconvertible and will not contribute to the number of stereoisomers. The most convenient method of designating the configuration of the stereoisomeric forms of XCI is by the relation of the hydrogen atoms on C_6 and C_{11} to the C_8 methylene bridge. There are six stereoisomeric forms, or three racemic pairs, of XCI. They are, with respect to the C_8 methylene bridge: (1) hydrogens on C_6 and C_{11} both *cis* to the bridge, (2) hydrogens on C_6 and C_{11} both *trans*, (3) hydrogen on C_6 *cis* and hydrogen on C_{11} *trans*. The structure in which the hydrogen on C_6 is *trans* and the hydrogen on C_{11} is *cis* to the C_8 methylene bridge is simply #3 rotated through 180°.

In the light of the prediction of the number of isomers of XCI, it is of interest to survey those $C_{15}H_{26}N_2$ stereoisomers which have been isolated or prepared. In addition to *d*- and *l*-sparteine ($[\alpha]_D \pm 17^\circ$ in ethanol), which together constitute one of the three racemates, a new isomer appears to have been formed by dehydrogenation of *l*-sparteine followed by rehydrogenation. (The assumption is made that the basic

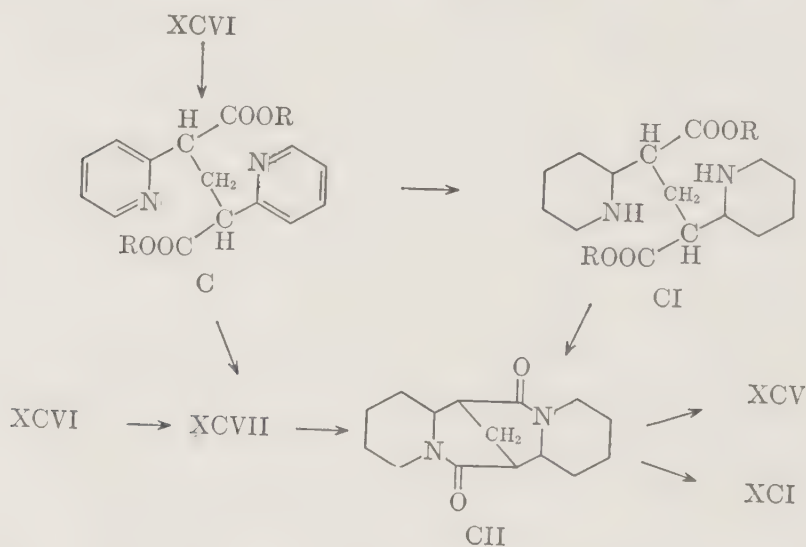
ring structure is unchanged.) Wolffenstein and Reitmann (264) obtained a "pseudosparteine," $C_{15}H_{26}N_2$ ($[\alpha]_D - 49.8^\circ$ in chloroform), by catalytic hydrogenation of their dehydrosparteine. The pseudosparteine was not fully characterized, but it appears to be identical with the " α -isosparteine" ($[\alpha]_D - 56.2^\circ$ in methanol) obtained by Winterfeld and Rauch (267). Their fully characterized solid product, m.p. 118° (picrate, m.p. 214° ; bisulfate, 244 – 245°), was obtained by catalytic hydrogenation of their α -didehydrosparteine, and an identical product, *l*- α -isosparteine has now been found in nature (310). With three of the stereoisomers of $C_{15}H_{26}N_2$ (XCI) accounted for, the disposition of the two bases of $[\alpha]_D - 17^\circ$ (ethanol) and $[\alpha]_D - 1.2^\circ$ (ethanol) isolated by Winterfeld and Nitzsche (271) from sparteine sulfate mother liquors, remains in doubt. The missing three stereoisomers of XCI can reasonably be expected to be a pair of enantiomorphs of as yet unknown specific rotation and a solid isomer, m.p. 118° , $[\alpha]_D + 56.2^\circ$ in methanol.

Two $C_{15}H_{26}N_2$ compounds were also isolated from sparteine sulfate mother liquors as obtained in the purification of the plant extracts (271) which are apparently structural isomers of XCI. These compounds, $[\alpha]_D - 13.58^\circ$ and 120.40° in ethanol, gave very strong pine splinter tests for the pyrrole ring. Moureu and Valeur (251) postulated that their "isosparteine," $[\alpha]_D^{18} - 25.0^\circ$ in ethanol (picrate, m.p. 178°), obtained by a Hofmann degradation and reversal, also contained a methylpyrrolidine ring.

c. Synthesis of Sparteine. The conversion of the alkaloid lupanine (XCIV) to sparteine (XCI) by Clemo and his coworkers (69, 259) actually constituted the first partial synthesis of sparteine, but it was not a total synthesis since lupanine had been isolated only from plant material. The total synthesis of sparteine has now been announced from five laboratories. Leonard and Beyler (272) found that the intermediate used by Clemo, Morgan and Raper (260) in their synthesis of oxysparteine (XCV), 1-carbethoxy-3-(α -pyridyl)-4-ketoquinolizine (1-carbethoxy-4-keto-3-(2'-pyridyl)-pyridocoline) (XCVII), could be converted to sparteine in one step. Compound XCVII was subjected to hydrogenation in dioxane solution over copper chromite catalyst at 250° and 350 atmospheres. The product was fractionated and a compound, $C_{15}H_{26}N_2$, was isolated which had all of the properties ascribed to *dl*-sparteine (monopicrate, m.p. 136 – 137° ; dipicrate, m.p. 208° ; oxidized by alkaline ferri-cyanide to *dl*-oxysparteine, m.p. 110 – 111°). The infrared spectra of the synthetic $C_{15}H_{26}N_2$ dipicrate and an authentic sample of *l*-sparteine dipicrate were identical in solution.

The preparation of *dl*-oxysparteine (XCV) by Clemo, Morgan, and Raper (260), in addition to furnishing structural proof of the C_{15} lupin

alkaloids, was also an approach toward the total synthesis of sparteine. Reduction of oxysparteine could not be accomplished with the reagents available at the time it was prepared; however, in 1948 Clemo, Raper, and Short (273, 274) reported a successful reduction of *l*-oxysparteine to *l*-sparteine by means of lithium aluminum hydride. The communications from Leonard's and from Clemo's laboratory were closely followed by another reported synthesis of sparteine when Sorm and Keil (275) announced the successful electrolytic reduction of two stereoisomerides of dioxosparteine (CII) (276, 277). Dioxosparteine was available through a series of reactions starting with the condensation of 2-pyridylacetic ester (XCVI) with formaldehyde or methylene iodide. The dimethyl 2,4-di-(α -pyridyl)glutarate obtained (C) was reduced catalytically to the corresponding saturated diester CI, which underwent dilactamization to dioxosparteine (CII). It is of interest that Galinovsky and Kainz



(277) were able to reduce only one of the carbonyl groups by hydrogenation over platinum in hydrochloric acid solution. The resulting product was *dl*-oxysparteine (XCI). Sorm and Keil (275) isolated two dioxosparteines by chromatography. One of the dioxosparteines, m.p. 172°, was reduced to a $C_{15}H_{26}N_2$ base (XCI) which formed a dipicrate of melting point 222°. The other dioxosparteine, m.p. 135°, after reduction gave two base dipicrates, m.p. 205° and 190°, which were separated mechanically. The free bases were not isolated. Analyses of the second pair of picrates did not check as well as might be expected, and on subsequent recrystallization the melting points fell to 201° and 178°. The dipicrate of melting point 205° was thought to be related to that of natural sparteine.

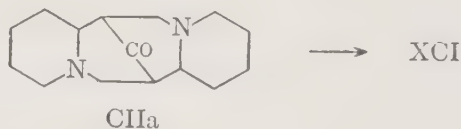
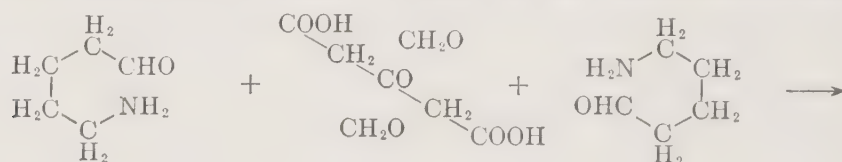
The synthesis of sparteine has been shortened to a simple two-step process by Leonard and Beyler (278). Both 1-carbethoxy-3-(α -pyridyl)-4-ketoquinolizine (XCVII) and diethyl 2,4-di(α -pyridyl)-glutarate (C) were available directly from ethyl 2-pyridylacetate (XCVI), and the remaining step involved combined cyclization and reduction of either precursor. The conditions employed for this second step were those of high temperature, high pressure hydrogenation over copper chromite. The method allowed the efficient preparation of *dl*-sparteine and also of *dl*- α -isosparteine. The latter product was fully characterized as a solid isomer of sparteine, $C_{15}H_{26}N_2$, m.p. 78–80° (monohydrate, m.p. *ca.* 100°; monopicrate, 132.5–133.5°; dipicrate, 222°; monoperchlorate, 160–162°). The dipicrate had the same melting point as Sorm and Keil's highest-melting picrate. Leonard and Beyler's *dl*- α -isosparteine was established as identical—by means of infrared absorption spectra and by physical properties—with the racemate of the *l*- α -isosparteine obtained by Winterfeld and Rauch (267), on hydrogenation of α -didehydrosparteine.

Although oxysparteine (XCV) was not readily reduced to sparteine by hydrogenation over platinum in hydrochloric acid solution, since XCV remained the product of such hydrogenation of dioxosparteine (CII) (277), this conversion of oxysparteine to sparteine was shown to be possible by electrolytic reduction (318, 319). *l*-Oxysparteine (presumably obtained by the oxidation of *l*-sparteine) was converted to *l*-sparteine by reduction, in fifty percent sulfuric acid solution, at a lead cathode using a current density of 0.12 amp./sq. cm. (318). Following this report, Galinovsky and Kainz (319) succeeded in resolving synthetic *dl*-oxysparteine by means of tartaric acid and converted both resolved forms of oxysparteine electrolytically to the corresponding forms of sparteine. The same workers were successful in reducing *dl*-10,17-dioxosparteine (CII) electrolytically to *dl*-sparteine (40% yield).

The resolution of synthetic *dl*-sparteine was achieved by Leonard and Beyler (278, 279) by means of *l*- and *d*- β -camphorsulfonic acid, and both optically active forms of sparteine were obtained. The free bases were not isolated but each enantiomorph was identified through the formation of two known derivatives. The derivatives used to identify *l*-sparteine were the *d*- β -camphorsulfonate and the dipicrate. The former salt was characterized by melting point, mixed melting point with an authentic sample, and specific rotation. The latter salt was characterized by melting point and mixed melting point with authentic *l*-sparteine dipicrate. *d*-Sparteine *l*- β -camphorsulfonate had a specific rotation equal and opposite to its enantiomorph *l*-sparteine *d*- β -camphorsulfonate. Characterization of *d*-sparteine was accomplished by conversion of the camphorsulfonate salt to the dipicrate and monoperchlorate, both of which were

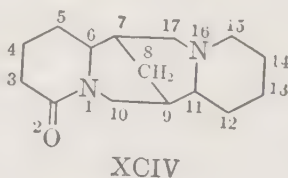
undepressed in melting point when mixed with the corresponding samples of natural *d*-sparteine dipicrate and monoperchlorate (7, 8, 19, 32). A further confirmation of the resolution was provided by infrared data. The infrared absorption spectra of natural *l*-, resolved *l*-, natural *d*-, and resolved *d*-sparteine dipicrates were found to be identical for these samples in the crystalline state.

Perhaps the most interesting synthesis of sparteine, especially from the biogenetic point of view, is due to Anet, Hughes, and Ritchie (317). By allowing acetonedicarboxylic acid and δ -aminovaleraldehyde to react in dilute aqueous solution at pH 13, followed by adjustment of the pH to 3 and addition of formaldehyde, 8-ketosparteine (CIIa) was produced in 30% yield. The conversion of CIIa to *dl*-sparteine was then accomplished by Clemmensen reduction in near quantitative yield.



4. LUPANINE, $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}$

Mention of lupanine (XCIV) has already been made in consideration of the structure proof of sparteine (XCI) and in relation to the vari-



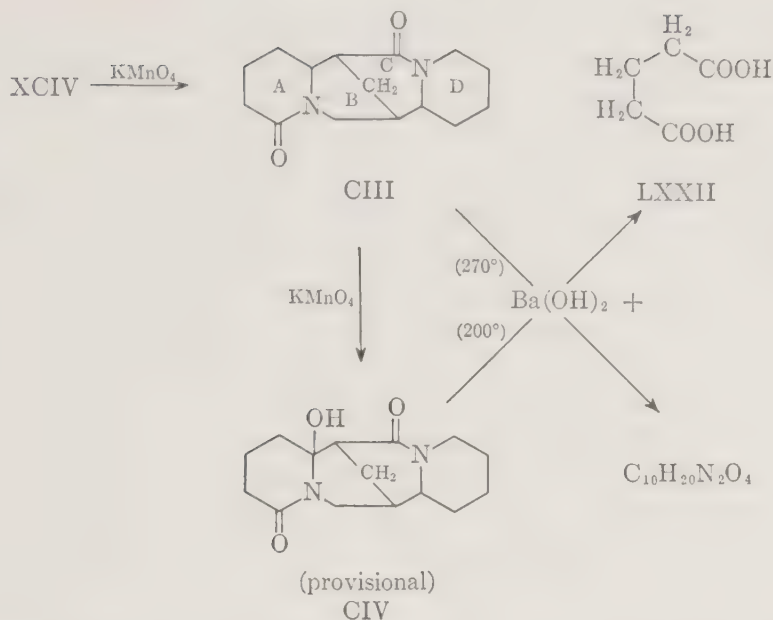
ous interconversions effected among the C_{15} lupin alkaloids. Both *d*- and *l*-lupanine have been found in plant sources, and the racemic mixture has also been identified, usually in the presence of excess of one of the optically active forms. Couch (280) has described a method for the separation of a mixture composed of *d*- and *dl*-lupanine. The *l*-form of lupanine and hydrorhombinine have been established as identical (68), and the *l*-form is also identical with tetrahydroanagyryne. Since there are four different asymmetric carbons in lupanine: 6, 7, 9, 11, but the C's bridge is necessarily fixed in a *cis* position, there should be four racemates, or eight optical isomers, represented by structure XCIV.

d-Lupanine has been characterized by a number of derivatives: monohydrochloride, m.p. 269–271° (65); dihydrochloride (monohydrate), 162–163° (65); monohydrobromide (dihydrate), 127° (55); monohydriodide, 189° (65); picrate, 185° (65); aurichloride, 205–206° (65); perchlorate, 211–212° (65); methiodide, 258° (62); mono-*d*- β -camphorsulfonate, 113–115° (65); di-*d*- β -camphorsulfonate, 245–246.5° (65). *l*-Lupanine forms a monohydriodide (dihydrate), m.p. 190° (259); thiocyanate, 183–185° (259); perchlorate, 213° (19), and it can be assumed that other salts would have the same melting points as the analogous *d*-lupanine derivatives. *dl*-Lupanine has been characterized as the monohydriodide (dihydrate), m.p. 184–185°; aurichloride, 177–178°; methiodide, 239–241° (55), and this racemate has been obtained by mixing the active forms (55), as well as from various plants. The racemic form was resolved successfully by Clemons, Raper, and Tenniswood by means of camphorsulfonic acid (259).

d-Lupanine was isolated from blue lupin seeds by Hagen (281) and was well characterized through the formation of salts. The correct molecular formula, $C_{15}H_{24}N_2O$, was assigned by Siebert (282), who also described the alkaloid's stability toward concentrated hydrochloric acid and aqueous potassium hydroxide. Distillation with soda lime gave ammonia and a pyridine base, but strenuous permanganate oxidation afforded no well-defined products. Soldaini (283) did similar isolation and characterization work on both racemic and *d*-lupanine. Schmidt (54) and Davis (55) showed the absence of a reactive carbonyl, hydroxyl, or methoxyl group in lupanine. Davis (55) and Beckel (58) indicated by titration and salt formation that lupanine was a monoacidic base but that the second nitrogen could react slightly basic, since certain diacid salts were formed. Beckel (59) also investigated oxidation products of lupanine with hydrogen peroxide and with alkaline permanganate, and found that lupanine perbromide gave a solid product when heated with ethanol, $C_{15}H_{23}N_2O \cdot OC_2H_5 \cdot 2HBr$, m.p. 227–228°, $[\alpha]_D^{18} - 129.4^\circ$ (water). The free base, ethoxylupanine, characterized also as the dihydriodide and dithiocyanate, could be reconverted to lupanine by the action of hydrogen iodide. A number of degradation processes were investigated by Thoms and Bergerhoff (284). Zinc dust distillation gave 2-ethylpyridine and another base of about double the molecular weight. Hofmann degradation was ineffective, and ring opening with cyanogen bromide was inconclusive at the first stage. Winterfeld and Kneuer (285) later obtained, by the action of cyanogen bromide on lupanine, bromolupanine cyanamide, $C_{15}H_{24}N_2O \cdot BrCN$ (m.p. 123°, $[\alpha]_D^{18} + 82.9^\circ$), and reduced this product to lupanine cyanamide. The nitrile group was removed by hydrolysis, and the resulting base, $C_{15}H_{26}N_2O$, was characterized as a secondary

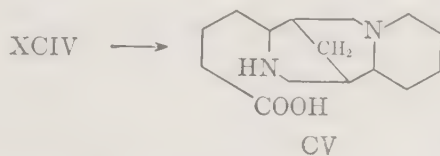
amine (aurichloride, m.p. 153°; picrate, 93–94°; platinichloride, 225°: *N*-benzoyl, 195°; *N*-benzoyl aurichloride, 206°). Phosphorous pentabromide and phosphorus pentachloride did not effect scission of the *N*-benzoyl derivative. The free base was methylated to give $C_{16}H_{28}N_2O$ (hydriodide, m.p. 277–278°; aurichloride, 140°), and a Hofmann degradation on this *N*-methyl compound gave trimethylamine at the second stage. Clemo and Leitch (69) applied the Hofmann degradation to lupanine. Distillation of lupanine methiodide over potassium sodium hydroxide furnished two *des-N*-methyllupanines, $C_{16}H_{26}N_2O$ (*alt.* methyllupanines (69)): α , m.p. 123°; hydrochloride, m.p. 209°; methiodide, m.p. 258°; β , oil; methiodide, m.p. 272°. Continuation of the degradation process led to anomalous results.

In the same paper, however, Clemo and Leitch (69) provided the key to the structure of lupanine, which had generally been assumed to be related to sparteine. They reduced *dl*-lupanine with phosphorus and hydrogen iodide to $C_{15}H_{26}N_2$, which they first called “deoxylupanine” and later identified as *dl*-sparteine (see page 160). Similar reduction of *d*-lupanine furnished *l*-sparteine, while *l*-lupanine gave *d*-sparteine (259). The synthesis of oxysparteine (XCV) by Clemo, Morgan, and Raper (260), combined with the reduction of anagryne, an α -pyridone (XCIII), to *l*-lupanine by Ing (6), definitely established the ring system of lupanine and the position of the lactam carbonyl in the A ring (XCIV). Oxidation products of anagryne and of lupanine were useful in turn for locating the lactam carbonyl of oxysparteine (XCV) in ring C rather than in ring B (258). In the first paper of the series, Clemo and Leitch (69) described oxylupanine, $C_{15}H_{22}N_2O_2$ (m.p. 123°; platinichloride, m.p. 232°), obtained by the cold permanganate oxidation of lupanine together with a by-product, “B”: $C_{15}H_{22}N_2O_3$, m.p. 233°. Oxylupanine was characterized as a neutral compound containing inert oxygen and nitrogen functions; therefore, there was no possibility of an imide-amine type of structure, but an amide-amide type was indicated (CIII). When oxylupanine (CIII) was treated with barium hydroxide at 270°, glutaric acid (LXXII) was formed (131). When an aqueous solution of oxylupanine was treated with potassium permanganate at 40–50°, a compound “A,” $C_{15}H_{22}N_2O_3$ (m.p. 212°), was obtained. Its production involved the insertion of an oxygen atom without removal of hydrogen, and the product did not react with phenyl isocyanate, nor did it give reactions of keto or reactive methylene groups. It did not liberate iodine from potassium iodide or revert to oxylupanine upon sulfurous acid treatment, hence it was not an amine oxide. When substance “A” was heated with barium hydroxide at 200° or 270°, glutaric acid (LXXII) was produced, as from oxylupanine. At 200°, a colorless crystalline compound, $C_{10}H_{20}N_2O_4$, m.p. 248°, and a



compound giving a picrate, m.p. 231° , were also produced. The same products were also obtained from oxylupanine and barium hydroxide at 270° . Clemo and Raper (258) argued later that substance "A" must have the second carbonyl group at C₁₇ and a tertiary hydroxyl group at C₆, and assigned the structure CIV. This structure would allow cleavage to a compound containing ten carbon atoms and to facile production of glutaric acid by the splitting out of C₂ to C₆.

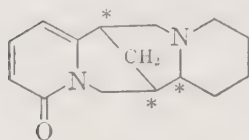
The existence of the piperidone ring A in lupanine was again demonstrated by Hoffmann, Holschneider, and Winterfeld (286), in the successful scission of this ring by hydrochloric acid in a sealed tube at 150° (*cf.* 282). The amino acid thus formed (CV) was characterized as the platinum-



chloride (m.p. 245°) of the ethyl ester. Winterfeld and his coworkers (266, 269, 270) also investigated extensively the action of Grignard reagents on the lactam group of the alkaloid.

5. ANAGYRINE, C₁₅H₂₀N₂O

Closely related to lupanine is the alkaloid anagyrine (XCIII), which has also been known as monolupine, rhombinine (68), and the "alkaloid III" of Orekhov and his coworkers (4). Marion and Ouellet (68) have



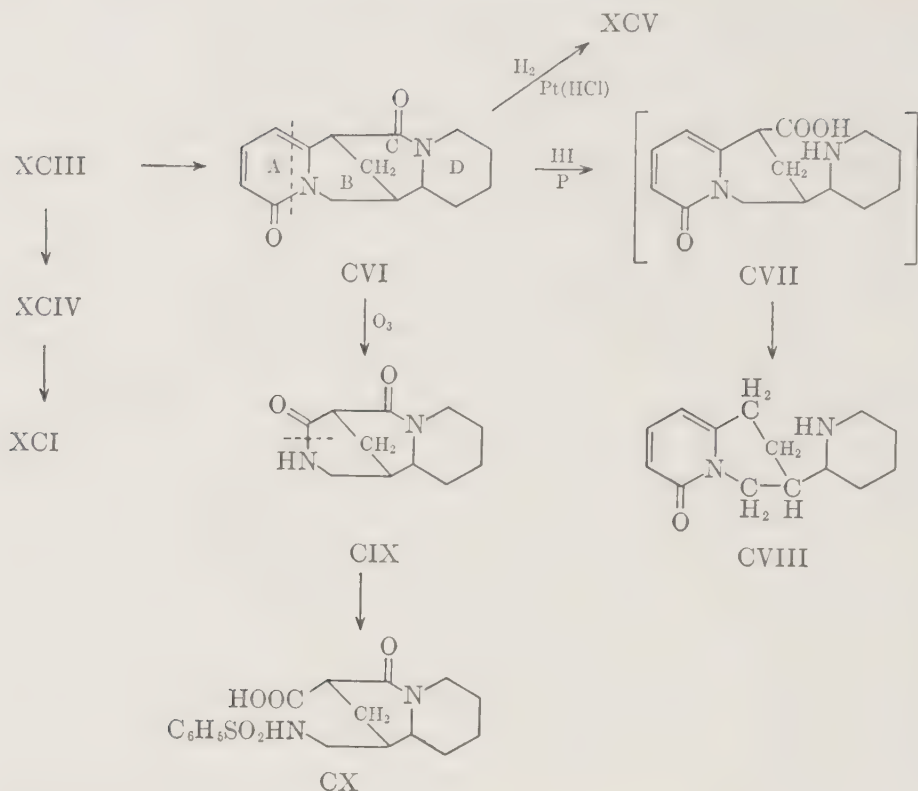
XCIII

shown the identity of rhombinine (18, 22) and monolupine (15) with anagryrine by direct comparison, by mixed melting points of corresponding derivatives, and by the identity of their infrared spectra. "Rhombinine" was reducible to *l*-lupanine and to *d*-sparteine, just as anagryrine (6). Only one form of anagryrine has been found in nature. The structural formula XCIII which contains three different asymmetric carbon atoms: 7, 9, 11, and a C_8 bridge which spans the distance between C_7 and C_9 in a *cis* fashion, can represent two racemates, or four optically active isomers. Anagryrine was isolated as an oil from *Anagryris foetida* by Partheil and Spasski (287), who made the aurichloride, m.p. 206–207°. Other salts which have served usefully for the characterization of the alkaloid are the following: picrate, m.p. 253° (68); picrolonate, 253° (20); perchlorate, 315° (19); methiodide, 262° (20); hydrochloride, 285° (68); mercurichloride, 230–232° (20); platinichloride, 280° (68); dibromoanagryrine, 202.5–203° (68, 288).

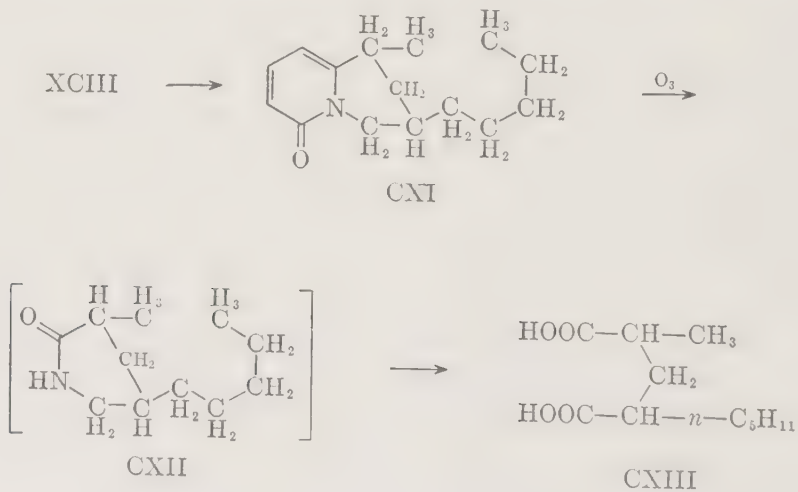
The similarity of anagryrine to cytosine (LXI) was early realized by Schmidt (289) and his students Litterscheid (193) and Klostermann (288). Both of the nitrogens present were tertiary, but since the alkaloid formed monoacid salts, one of the nitrogens was considered nonbasic and tests indicated that the oxygen function was inert. Anagryrine like cytosine was readily brominated, with the resulting replacement of two of its hydrogens by bromine (288). So similar were the alkaloids anagryrine and cytosine, that Litterscheid (193) synthesized four isomeric *N*-butylcytosines for comparison with anagryrine. This work was done on the assumption of the formulas $C_{11}H_{14}N_2O$ for cytosine and $C_{15}H_{22}N_2O$ for anagryrine (C_4H_8 difference). The latter was subsequently shown to be incorrect by Ing, who established the molecular formula as $C_{15}H_{20}N_2O$ (6). The difficulty facing the early investigators was that of the separation of anagryrine from cytosine, since the two usually occurred together in plant material. Ing (6) found that anagryrine is more readily extracted by benzene from its aqueous solution than cytosine and that its perchlorate is much less water-soluble than that of cytosine. The composition $C_{15}H_{20}N_2O$ assigned to anagryrine was amply supported by the analysis of its derivatives.

Anagryrine gave a red color with ferric chloride. It formed a dibromoanagryrine, $C_{15}H_{18}Br_2N_2O$, m.p. 202–203°, which was reconverted to anagryrine by zinc dust and acetic acid but did not lose hydrogen

bromide during boiling with alcoholic potassium hydroxide. It was reduced with difficulty, but catalytic hydrogenation over palladized charcoal at 80–90°C. in acetic acid converted anagryne to tetrahydroanagryne, $C_{15}H_{24}N_2O$. This product was proved to be identical with *l*-lupanine (XCIV) (259) since the rotations of the two bases were identical, as were the melting points and rotations of the hydriodides and thiocyanates. Anagryne was reduced electrolytically in sulfuric acid at a lead cathode to hexahydrodeoxyanagryne, $C_{15}H_{26}N_2$, which, although its specific rotation was somewhat low, formed a dipicrate which was identical with authentic *d*-sparteine dipicrate and formed a monohydriodide and a monoperochlorate which had properties identical with those of the *l*-sparteine derivatives. The identity of hexahydrodeoxyanagryne with *d*-sparteine (XCI) was thereby established. Oxidation of anagryne by barium permanganate gave a crystalline product, $C_{15}H_{18}N_2O_2$, m.p. 201–202°, very probably identical with Litterscheid's anagryne oxide, m.p. 195° (aurichloride, m.p. 225°; platinichloride, m.p. 240°) (193). It was named "anagryamide" by Ing (6) because of analogy with the *N*-methylcytisamides (183), but it was later called "oxyanagryne" by Galinovsky and Stern (188). The structure of anagryamide was assigned (CVI) on the basis of further degradation reactions (6). It contained no hydroxyl or ketone group, did not form a methiodide, and was remarkably stable to hydrolytic agents. However, on treatment with red phosphorus and hydriodic acid at 240°, a new secondary base was formed: anagryamine, $C_{14}H_{20}N_2O$, m.p. 98–99° which was characterized by nitroso (m.p. 127–128°) and acetyl (m.p. 134–135°) derivatives. The conversion of anagryamide to anagryamine involves the hydrolysis of a lactam grouping and the decarboxylation of the acid thus formed. Since facile decarboxylation is a property associated with pyridine-2-acetic acids (183, 184), formula CVII would satisfactorily represent the intermediate amino acid and formula CVIII, the anagryamine. On ozonization, anagryamide lost C_4H_2 and a new lactam, $C_{11}H_{16}N_2O_2$, m.p. 258°, was formed. The loss of C_4H_2 in this reaction was analogous to a similar loss observed by Späth and Galinovsky (181) working in the cytisine series. Taken in conjunction with the color reactions of anagryne and its reduction and bromination products, the accumulated evidence pointed definitely to an α -pyridone ring in anagryne. The lactam $C_{11}H_{16}N_2O_2$ formed on ozonization was hydrolyzed, and a benzenesulfonyl derivative was formed from the resulting amino acid: $C_{17}H_{22}N_2O_5S$, m.p. 141° with effervescence. Since the benzenesulfonyl derivative lost carbon dioxide readily at the melting point, it was evidently a malonyl type compound, and the structure CX was assigned to the benzenesulfonamido acid, and CIX, to the lactam precursor. The accumulated evidence indicated the α -pyridone



nature of ring A and the presence of a lactam group in ring C. In order to obtain more complete data as to the total structure of the anagryne molecule and especially as to the nature of ring D, anagryne was subjected to exhaustive methylation, followed by catalytic reduction at each stage. After trimethylamine was liberated at the third stage and the residue had been distilled and hydrogenated, a feebly basic oil, $C_{15}H_{23}NO$,



b.p. 155–160° (4 mm.), was obtained. This compound was called hexahydroanagyryline and was assigned the structure CXI on the basis of its ozonization reaction. The lactam produced on ozonization (CXII), $C_{11}H_{21}NO$, b.p. 140–150° (4 mm.), was hydrolyzed by hydrochloric acid and the resulting amino acid was not isolated but was oxidized directly to an amorphous dicarboxylic acid, $C_{11}H_{20}O_4$, which yielded a crystalline imide, m.p. 58–60° (6, 290). By subjecting tetrahydrohemicytisylene, in the cytisine series, to similar degradation, Späth and Galinovsky (181) obtained $\alpha\alpha'$ -dimethylglutaric acid, and on the basis of XCIII for anagyryne, hexahydroanagyryline should yield α -methyl- α' -amylglutaric acid (CXI \rightarrow CXII \rightarrow CXIII). Synthetic α -methyl- α' -*n*-amylglutarimide (mixed *cis* and *trans*) had the same melting point alone, or mixed with the imide obtained from the alkaloid, as did the latter (58–60°). Pure *cis*- α -methyl- α' -*n*-amylglutarimide, synthesized by Rydon (290) melted at 71–72° and raised the melting point of the imide from anagyryne to 59–64°. The production of α -methyl- α' -*n*-amylglutaric acid by the degradation of anagyryne indicated that ring D was either piperidine or α -methylpyrrolidine, and that it was six membered was definitely established when Clemo, Morgan, and Raper (260) synthesized oxysparteine, since oxysparteine, sparteine, anagyryne and lupanine were known to have the same ring structure. Oxysparteine (XCV) was later related directly to anagyryne when Galinovsky and Stern (188) showed that anagyramide (oxyanagyryne) (CVI) could be hydrogenated over platinum in hydrochloric acid solution to *d*-oxysparteine. In this reduction, the α -pyridone ring was attacked, but the lactam group of the inner ring was unchanged. Since the carbonyl group in anagyramide (oxyanagyryne) was shown to be in ring C by the work of Ing (6), the reduction of anagyramide to oxysparteine proved that the carbonyl group in oxysparteine was likewise in ring C. This information was important in the assignment of structures to other alkaloids which were isomers of lupanine (as is oxysparteine).

6. ALKALOIDS RELATED TO SPARTEINE

It appears useful for discussion purposes to group most of the minor lupin alkaloids on the basis of their similarity—in constitution, molecular formula, or derivation—to the three C_{15} alkaloids about which most is known: sparteine, lupanine, and anagyryne. The groupings should not be considered inflexible nor should they be considered to have more significance than that of general similarity. On this basis, aloperine, pusilline, and retamine are considered to be related to sparteine. The melting point and rotation for each alkaloid can be found in Table 1, along with the plant source.

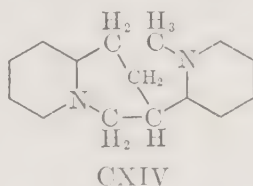
a. *α -Isosparteine*, $C_{15}H_{26}N_2$. This isomer of sparteine, first obtained by partial synthesis from sparteine, by dehydrogenation using mercuric acetate followed by catalytic rehydrogenation of the α -didehydrosparteine (253, 267, 268), was shown to have the same ring structure as sparteine (XCI), and therefore to be a stereoisomer. *l*- α -Isosparteine was thereby obtained from *l*-sparteine and a number of derivatives have been employed for characterization: monohydrate, m.p. 98–115° and $[\alpha]_D^{30} - 55.8^\circ$ (methanol) (278); dipicrate, m.p. 221° (d.) (278); bisulfate, m.p. 267° (d.) (278); diperchlorate, m.p. 262–263° (310). A second partial synthesis of α -isosparteine was realized in the conversion, by catalytic hydrogenation, of the alkaloid *d*-thermospine (see below) to *l*- α -isosparteine, and *l*-thermopsine to *d*- α -isosparteine (315). A total synthesis of *dl*- α -isosparteine was effected in the process of Leonard and Beyler (278) for the synthesis of *dl*-sparteine, since an isomer accompanied the sparteine in the product and was definitely identified as *dl*- α -isosparteine by means of infrared absorption spectra comparison. The *dl*- α -isosparteine, m.p. 78–80°; hydrate, m.p. 98–105°, was characterized by the formation of salts: monopicrate, m.p. 132.5–133.5°; dipicrate, 222–223°; monopерchlorate, 160–162°. It appears likely that the dipicrate, m.p. 222°, obtained by Sorm and Keil (275) *via* electrolytic reduction of the *dl*-dioxosparteine of m.p. 172°, was that of *dl*- α -isosparteine, although no direct characterization was provided.

Following the partial and total syntheses of α -isosparteine, the natural occurrence of *l*- α -isosparteine in *Lupinus caudatus* Kellogg was definitely established (310). More recently, the identity of *l*- α -isosparteine with "genisteine" has been confirmed (312). Genisteine was first considered, erroneously, to be an alkaloid of composition $C_{16}H_{28}N_2$ (45, 46, 271), isolated from *Cytisus scoparius* L. For direct comparison and identification, recourse was had to additional derivatives: aurichloride, m.p. 199° (d.); platinichloride, m.p. 276–278° (d.), and to infrared absorption spectra (312).

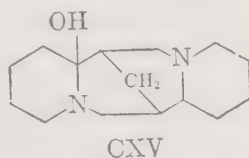
b. *Aloperine*, $C_{15}H_{24}N_2$. The molecular formula $C_{15}H_{24}N_2$ has been assigned to this alkaloid on the basis of analyses of a number of salts: dihydrochloride, m.p. 261–263°, $[\alpha]_D \mp 92.4^\circ$ (water); hydriodide, 242–244°; picrate, 235° (d); picrolonate, 190–195°; aurichloride, 204–206° (1). Accordingly, aloperine is isomeric with spartyrine and sarothamnine. Both nitrogens are basic, as indicated by the formation of mono- and diacid salts, and one of the nitrogens is secondary, as indicated by the formation of *N*-benzoylaloperine (m.p. 161–162°) and *N*-methylaloperine methiodide (m.p. 190–195°; hydriodide, m.p. 247–249°) (1).

c. *Pusilline*, $C_{15}H_{28}N_2$. Pusilline (perchlorate, m.p. 219.5°; methiodide, m.p. 260°) differs from sparteine by two more hydrogen atoms (19).

Marion and Fenton found that its properties were closely related to those of sparteine, from which it was difficult to separate the alkaloid. In common with sparteine, pusilline formed a monoperochlorate which crystallized from aqueous solution only after the addition of a little ammonia. Pusilline was found to contain one methylimino group, and it formed a methiodide which did not undergo the Hofmann degradation but was reconverted to the original base. On the basis of these facts, one probable structural formula for pusilline would be CXIV. It appears that two compounds previously described as the alkaloids nonalupine (90) and spathulatine (90, 108) are in essence derivatives of pusilline (309).



d. Retamine, $C_{15}H_{26}N_2O$. Retamine, first isolated by Battandier and Malosse (93, 94), was found by White (37) to give microscope slide reactions similar to those of sparteine and monspessulanine (12). A number of derivatives have been prepared which indicate the nature of the nitrogens: dihydrochloride, m.p. 298° ; dipicrate (monohydrate), $167-170^\circ$ (328); monomethiodide, 217° ; acetate (hygroscopic), *ca.* 60° ; phenylurethane, $190-191^\circ$. White suggested that retamine was probably a hydroxysparteine, and Ribas, Sanchez, and Primo (95) suggested further that it was probably 6-hydroxysparteine (CXV). Retamine exerted



no reducing power and the "tertiary" alcohol group could not be dehydrated readily. One active hydrogen was found and the alkaloid formed a benzoyl derivative (330). Treatment with phosphorus and hydrogen iodide, followed by treatment with zinc produced *d*-sparteine (329).

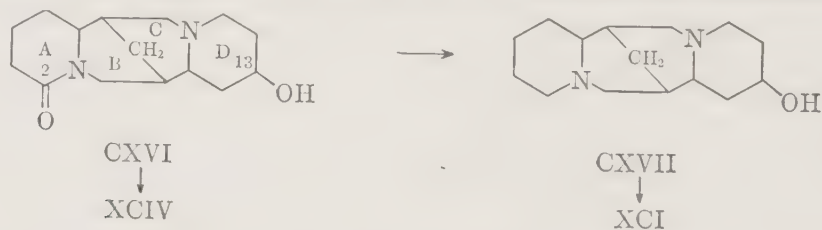
7. ALKALOIDS RELATED TO LUPANINE

a. α -Isolupanine, $C_{15}H_{24}N_2O$. The ring structure of this isomer of lupanine was established by its reduction to *l*- α -isosparteine by means of lithium aluminum hydride, and the position of attachment of the oxygen was decided by the identity of the infrared absorption spectrum of the $C_{15}H_{24}N_2O$ alkaloid with that of tetrahydrothermopsine (see below) (310). *d*- α -Isolupanine is therefore a diastereoisomer of *d*-lupa-

nine, and both are represented by the general structure XCIV. *d*- α -Isolupanine forms a picrate, m.p. 197–198° (310); perchlorate, m.p. 247–249° (d.); aurichloride, m.p. 195.5–196.5° (311); platinichloride, m.p. 238.5–240.5° (311).^{*} A partial synthesis of *d*- α -isolupanine has been accomplished by Marion and Leonard (320) by mercuric acetate dehydrogenation of *d*-lupanine followed by catalytic hydrogenation of the $C_{15}H_{22}N_2O$ intermediate.

b. $C_{15}H_{24}N_2O$. An alkaloid with this composition and a specific rotation of 25° (ethanol) was isolated by White (39), but it was found that it consisted of a mixture of *dl*-lupanine with excess of the *d*-form.

c. *Hydroxylupanine*, $C_{15}H_{24}N_2O_2$. This alkaloid (hydrochloride, m.p. 275° (50); aurichloride, 210° (50); picrolonate, 174–175° (50); hydriodide monohydrate, 91–93° (52); thiocyanate monohydrate, 125° (52)) was first isolated by Bergh (52), who showed its relation to *d*-lupanine by hydriodic acid reduction. Hydroxylupanine has been shown (309) to be identical with the "octalupine" of Couch (91, 291). The presence of a tertiary basic nitrogen was indicated by the formation of a methiodide, m.p. 228–230.5° (52) (Ueno (48) describes two methiodides: m.p. 238–239° and 236–239°), and by titration as a monoacid base (49). The presence of a hydroxyl group was indicated by the formation of an acetyl derivative (aurichloride, m.p. 211–211.5°) and a benzoyl derivative, m.p. 199–199.5° (48). Beckel (49) repeated and confirmed Bergh's reduction of hydroxylupanine to lupanine by the use of phosphorus and hydrogen iodide, and since lupanine has no *C*-methyl group, it is difficult to interpret the formation of an oxidation product of lupanine described as an aldehyde, $C_{15}H_{22}N_2O_2$ by Ueno (48). The functionality of the hydroxyl group was determined as secondary by Galinovsky and Pöhm (321), following their conversion of (*d*-)hydroxylupanine (CXVI) to *d*-lupanine (XCIV) by phosphorus pentoxide dehydration and subsequent



catalytic hydrogenation of the unisolated intermediate. The lactam carbonyl of hydroxylupanine was removed by hydrogenation of CXVI

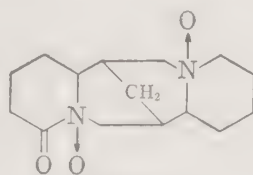
^{*} Due to the similarity of physical constants for *d*- α -isolupanine and its derivatives with the corresponding values for a $C_{15}H_{24}N_2O$ alkaloid from *L. angustifolius* described by Alfred Kneuer (Dissertation, "Zur Kenntnis des Lupanins. Lupanidine, ein neues Lupinenalkaloid," Freiburg i. B., 1929) and called lupanidine, it appears that the two may possibly be identical.

over platinum in hydrochloric acid solution to give (*l*-)hydroxysparteine, $C_{15}H_{26}N_2O$, m.p. 154–155°, $[\alpha]_D^{20} - 25.4^\circ$ (ethanol); dipicrate, m.p. 198°; monomethiodide, m.p. 230–232° (d.). The relation of hydroxysparteine (CXVII) to *l*-sparteine (XCI) was established by successive dehydration and hydrogenation, a reaction sequence parallel to that used for interrelation of CXVI and XCIV. The hydroxyl group in hydroxysparteine (CXVII) was shown to be secondary by Oppenauer oxidation of CXVII to a ketosparteine, $C_{15}H_{24}N_2O$ (hydrate, m.p. 87°), which formed an oxime, m.p. 244–245°.

The position of attachment of the hydroxyl group in hydroxylupanine (CXVI) and its congeners was assigned as C_{13} (C_{12} on the Couch system of numbering) by Galinovsky, Pöhm, and Riedl (322) on the basis of oxidation products obtained by exhaustive oxidation by chromic acid. Sparteine and lupanine gave more succinic acid by comparison, respectively, than hydroxysparteine and hydroxylupanine. The difference was thought to be due to the fact that ring D in CXVI and CXVII, with the hydroxyl located three carbons from the nitrogen, would not give succinic acid. The amino acids obtained by chromic acid oxidation of the four precursors were determined by paper chromatography (322). Sparteine and lupanine both furnished γ -aminobutyric acid, while hydroxylupanine and hydroxysparteine furnished β -alanine but no γ -aminobutyric acid. The fact that no γ -aminobutyric acid was isolated from the latter two compounds was taken as an indication that the chain of three unsubstituted carbons in ring D (C_{13} , 14, 15) of sparteine and lupanine must be interrupted by substitution at C_{13} in CXVI and CXVII.

d. $C_{15}H_{24}N_2O_2$. An alkaloid of this composition was isolated by Couch (65) from *Lupinus laxus* Rydb. It is isomeric with hydroxylupanine, but differs in melting point, water content, and optical activity.

e. *Trilupine*, $C_{15}H_{24}N_2O_3$. This is the di-amine oxide of *d*-lupanine and is associated with the latter alkaloid in *Lupinus laxus* (65). The alkaloid has been obtained anhydrous, m.p. 256–257°, and as the dihydrate, m.p. 128–129° (aurichloride, m.p. 198.5–199.5°; platinichloride (tetrahydrate), m.p. 224° (d.); picrate, m.p. 180–183°). Trilupine could be converted to *d*-lupanine by the action of acids and heat and can be prepared from the latter by reaction with calcium peroxide. It is therefore regarded (65, 292) as *d*-lupanine N,N' -dioxide (CXVIII).

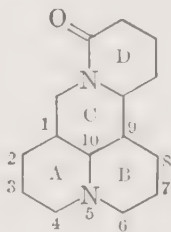


CXVIII

When trilupine was treated with methyl iodide in the cold, a compound was obtained, $C_{15}H_{24}N_2O_2 \cdot CH_3I$, m.p. 127° , which contained one oxygen atom less than required for trilupine methiodide and which appeared to be the methiodide of *d*-lupanine *N*-oxide. Ochiai, Ito, and Maruyama (292) prepared *d*-lupanine *N*-oxide by the action of 3% hydrogen peroxide on *d*-lupanine and described its methiodide as decomposing at 137° .

f. Sophocarpine, $C_{15}H_{24}N_2O$. The structure of this alkaloid (monohydrate, m.p. $81-82^\circ$ (82), $[\alpha]_D - 26.4^\circ$ (ethanol) (99); hydrobromide, m.p. $>250^\circ$ (99); hydriodide, $>300^\circ$ (82); methiodide, $200-202^\circ$ (82); picrate, $155-157^\circ$ (82); aurichloride, $166-170^\circ$ (82); platinichloride, $209-212^\circ$ (82)), which is isomeric with lupanine, has not been established. Like lupanine, but unlike the isomeric matrine, sophocarpine could be reduced electrolytically. The product of electrolytic reduction was $C_{15}H_{26}N_2$, b.p. $153-154^\circ$ (5 mm.), which differed from isomeric *l*-sparteine in that it was more levorotatory ($[\alpha]_D - 26.2^\circ$ in ethanol) and formed a dimethiodide (m.p. $>260^\circ$) (99).

g. Matrine, $C_{15}H_{24}N_2O$. This isomer of lupanine was first isolated by Nagai, who also assigned the correct molecular formula (see 79). The identity of matrine and "sophocarpidine" has been firmly established by Orekhov and Proskurnina (80). It has been shown by Ochiai and others (292, 293) that matrine and lupanine are definitely not stereoisomers but are structural isomers. Matrine exists in four forms as indicated in Table 1. Some of them have been interconverted (294). For example, from a petroleum ether solution of the β -form, a mixture of α - and δ -forms crystallizes at $22-24^\circ$. From a petroleum ether solution of the α -form, the β -form crystallizes at 10° . Isomeric methiodides of matrine, m.p. 254° (d.) and $>304^\circ$, have been described (84). Other derivatives which have been prepared are the hydrobromide, m.p. $272-275^\circ$ (84); aurichloride, $199-200^\circ$ (40); platinichloride, $229-230^\circ$ (40) or 249° (294); perchlorate, $214.5-216^\circ$ (84); methyl methylmatrinatate methiodide, $214-216^\circ$ (83) or 219° (294). Although the structure of matrine has not been rigorously established, the structural representation favored by Tsuda



CXIX

(295) is CXIX. The suggested grouping is unusual for the lupin alkaloids, since in sparteine, lupanine, and anagryne the third and fourth

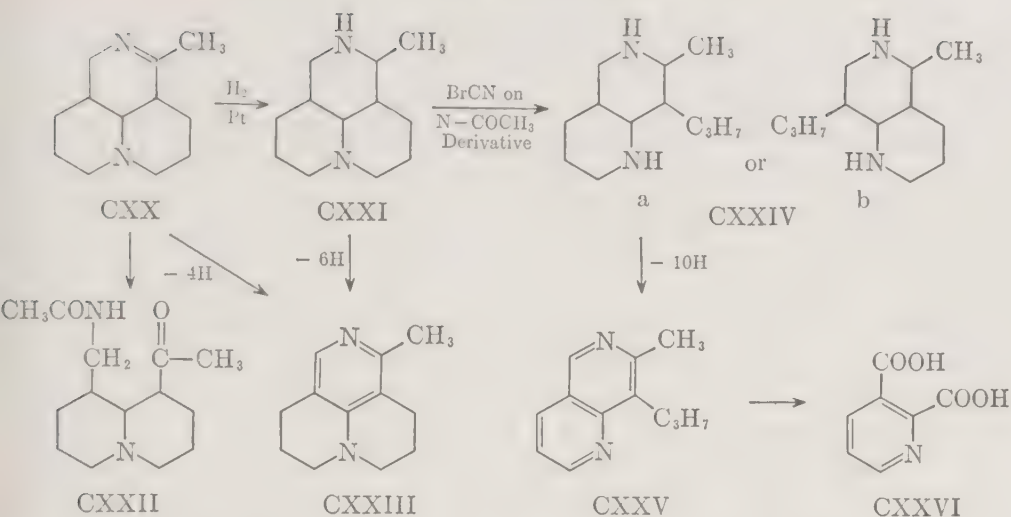
rings are created by junction at the 1- and 3-positions of quinolizidine. In the proposed formula for matrine, by contrast, the third and fourth rings are created by junction at C₁ and C₉.

The nature of the two nitrogen atoms present in matrine was revealed by the fact that there was no imino group or N—CH₃ group in the molecule. The alkaloid formed monoacidic salts, so that of the two tertiary nitrogens, one was an amine function and the other an amide function (294). The lactam group differed from that in the isomeric lupanine since it was not readily reduced by phosphorus and hydriodic acid or by hydrogen over platinum oxide in acetic acid solution (296), nor was it readily converted to the corresponding thioamide (292). The presence of the lactam group in matrine was definitely established by hydrolysis in potassium hydroxide to potassium matrinate, C₁₅H₂₅N₂O₂K, m.p. 239° (294). The amino acid, matrinic acid (m.p. 222° (d.), $[\alpha]_D^{10} + 19.87^\circ$ (water); aurichloride, m.p. 181°; platinichloride, m.p. 245° (d.)), was liberated from the potassium salt and the presence of a new secondary nitrogen in this compound was indicated by the positive Liebermann nitroso reaction. Matrinic acid could be reconverted to matrine by heat or by treatment with 2% hydrogen chloride in ethanol. When potassium matrinate was treated with methyl iodide, this reagent reacted with the potassium carboxylate group, the imino group, and one of the then two tertiary amino groups, so that methyl methylmatrinate methiodide, C₁₇H₃₀N₂O₂·CH₃I, m.p. 219°, was obtained. Further treatment with methyl iodide at 100° gave a dimethiodide, m.p. 145–146°, from which the monomethiodide could be regenerated by means of potassium carbonate. Methyl methylmatrinate (b.p. 210–212° (10 mm.), $[\alpha]_D^{15} - 21.23^\circ$) was made available by the action of heat on the corresponding methohydroxide. Kondo, Ochiai, and Nishimura (297) found that methylmagnesium iodide converted methyl methylmatrinate to a tertiary alcohol. The product resulting from the sodium and amyl alcohol reduction of matrine was not well defined, but the zinc dust distillation of matrine hydrochloride produced a small amount of an isomer of sparteine: matridine, C₁₅H₂₆N₂, m.p. 76°; aurichloride, m.p. 126° (294). Matrine was not affected by mercuric acetate or by cyanogen bromide (296).

The nature of rings A and B in matrine (CXIX) was indicated mainly by soda-lime and by zinc dust distillation experiments. Thus, matrinic acid hydrochloride gave, among other products of zinc dust distillation, a tertiary optically inactive base, C₁₀H₁₉N, characterized by a number of salts: mercurichloride, m.p. 206°; pierate, 165°; aurichloride, 143–144°; platinichloride, 216–217°; methiodide, 241° (294). Winterfeld and Kneuer (285) proved, by direct comparison with an authentic sample,

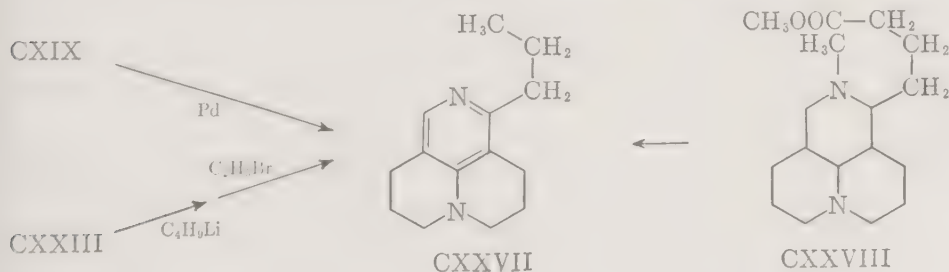
that the $C_{10}H_{19}N$ base was β -lupinane (1-methylquinolizidine) (XV). The same product was obtained by the zinc dust distillation of both α -matrinidine, $C_{12}H_{20}N_2$ (298), and β -matrinidine, $C_{12}H_{16}N_2$ (299), products, in turn, of the soda lime distillation of potassium matrinate (294, 300). The soda lime distillation of potassium matrinate also produced a fraction, b.p. $55-90^\circ$ (14 mm.), which was hydrogenated catalytically to a mixture of quinolizidine (I) and α -*n*-butylpiperidine (301). Both components were properly identified by mixed melting points of selected derivatives with those of authentic samples. The formation, indirectly from matrine, of 1-methylquinolizidine, quinolizidine, and α -*n*-butylpiperidine accounted for rings A and B of matrine (CXIX) with at least one carbon atom attached to the quinolizidine portion, and at C_1 .

The nature and location of ring C in matrine proved more difficult to ascertain. Again drastic degradation experiments provided the clues. Soda lime distillation of potassium matrinate gave two interesting C_{12} compounds: α -matrinidine, $C_{12}H_{20}N_2$ ($[\alpha]_D^{18} - 18.75^\circ$; picrate, m.p. 228°), and β -matrinidine, $C_{12}H_{16}N_2$ (practically optically inactive; picrate, m.p. 184°) (294, 301). α -Matrinidine was unsaturated and could be hydrogenated over palladium on charcoal or platinum to give dihydro- α -matrinidine, $C_{12}H_{22}N_2$, m.p. 66° (dihydrobromide, m.p. $136-137^\circ$; *N*-*p*-nitrobenzoyl derivative, m.p. $135-136^\circ$). The two matrinidines were interrelated by zinc dust distillation. This treatment converted α -matrinidine to a mixture of β -lupinane (XV), dihydro- α -matrinidine, and β -matrinidine (298), and converted β -matrinidine (dehydro- α -matrinidine) to a mixture of β -lupinane and dihydro- α -matrinidine (299). Dihydro- α -matrinidine was also obtained from α -matrinidine by electrolytic reduction (302). The acetyl derivative, $C_{14}H_{24}N_2O$, could be made normally and readily from dihydro- α -matrinidine (302), but α -matrinidine itself behaved abnormally with acetylating agents to give $C_{14}H_{24}N_2O_2$ (m.p. 160°). This product resulted from the addition of an acetyl group and water to the molecule (294). It turned out to be a δ -acetyl amino ketone, and a semicarbazone, d.p. 203° , was prepared as a derivative of the carbonyl function (295). The ready loss of four hydrogen atoms from α -matrinidine and six from dihydro- α -matrinidine under dehydrogenation conditions, with the formation of dehydro- α -matrinidine, was indicative of a piperidine ring in the dihydro compound, and the structure CXXI was accordingly suggested for dihydro- α -matrinidine (293). This would fix the structure of α -matrinidine as CXX, and accordingly the acetylation reaction with CXX would produce, not unexpectedly, the ketonic compound CXXII. The presence of an active methyl group, as represented in the formula (CXXIII) for the inactive dehydro- α -matrinidine, was indicated by the fact that this compound

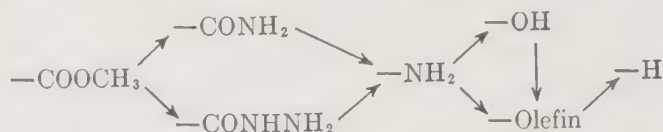


formed a benzal derivative (m.p. 106–107°) (293) and a lithium derivative (295). The cyanogen bromide degradation of acetyldihydro- α -matrinidine (301, 302) provided useful subsidiary information. A product, $\text{C}_{12}\text{H}_{24}\text{N}_2$ (m.p. 42–45°), was obtained which was shown to be a secondary-secondary diamine (bis-*p*-nitrobenzoyl derivative, m.p. 240–241°; picrate, m.p. 163–164° (d.)). It was formulated as CXXIV (a or b) since it lost ten hydrogen atoms when heated with palladium on asbestos at 270–310° to give $\text{C}_{12}\text{H}_{14}\text{N}_2$ (picrate, m.p. 189°), and the $\text{C}_{12}\text{H}_{14}\text{N}_2$ dehydrogenation product (CXXV) was oxidized by permanganate to quino-*linic* acid (CXXVI). A number of related compounds were also produced by this von Braun cyanogen bromide degradation of acetyldihydro- α -matrinidine.

Dehydrogenation of matrine itself was somewhat useful in enabling a decision as to the nature of the C and D rings. When matrine was heated with palladium on asbestos at 280–310°, two main products were produced: $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}$, octadehydromatrine, and $\text{C}_{14}\text{H}_{20}\text{N}_2$. The octadehydromatrine was a light yellow, optically inactive solid, m.p. 175–177°, which gave color reactions characteristic of an α -pyridone (296). The $\text{C}_{14}\text{H}_{20}\text{N}_2$ product was a liquid tertiary-tertiary diamine which formed monoacidic salts (hydriodide, m.p. 193–194.5°; hydrochloride, 208°;



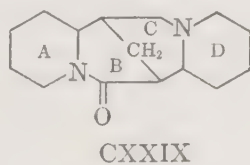
aurichloride, 118°; picrate, 142°; methiodide, 129°). It was related to dehydro- α -matrinidine (CXXIII) by synthesis. Compound CXXIII was treated with butyllithium and its lithium derivative was then condensed with ethyl bromide. The $C_{14}H_{20}N_2$ product was established as identical with that obtained by dehydrogenation of matrine (295). This partial construction of ring D served also as the meeting point for study on the partial degradation of ring D of the alkaloid. The carbomethoxyl group of methyl methylmatrinatate (CXXVIII) was converted by Hofmann hypobromite degradation on the amide (295) or by Curtius degradation on the hydrazide (303) eventually to a hydrogen (304):



The final stage in this conversion, reduction of the olefin "descarbonylmethylmatrinene," $C_{15}H_{26}N_2$, by means of phosphorus and hydriodic acid not only reduced the double bond but removed the *N*-methyl group. The product, "descarbonylmatrane," $C_{14}H_{26}N_2$, was dehydrogenated over palladium on asbestos with the resulting formation of "dehydrodescarbonylmatrane," $C_{14}H_{20}N_2$. By direct comparison (293, 295), this compound was proved to be identical with that (CXXVII) obtained by dehydrogenation of matrine and by extension of the side-chain of dehydro- α -matrinidine. Oxidation of dehydrodescarbonylmatrane methohydroxide with permanganate gave *n*-butyric acid. This product had to come from the *n*-propyl side-chain (from the lactam ring) since matrine methohydroxide gave no such product on permanganate oxidation (293). Further evidence for a piperidone ring D was found in the permanganate oxidation of methyl methylmatrinatate methohydroxide, which produced glutaric and succinic acids, but no methylsuccinic acid.

h. Oxymatrine, $C_{15}H_{24}N_2O_2$. Oxymatrine has been isolated from natural sources and has been synthesized by the action of hydrogen peroxide on matrine. It forms a monohydrate, m.p. 162–163° (d.) and the following salts (92): perchlorate, d.p. 240°; picrate, 215–216°; aurichloride, 208°; platinichloride, 250°; hydrobromide, m.p. 215°. Ochiai and Ito (305) found that phosphorus and hydriodic acid, sulfur dioxide, and acidic potassium iodide solution all converted oxymatrine to matrine and that the reverse change was possible with hydrogen peroxide. They showed thereby that oxymatrine was matrine *N*-oxide. Ethanolic potassium hydroxide converted oxymatrine to potassium oxymatrinatate (d.p. 195°), from which oxymatrinic acid was obtained as a monohydrate (d.p. 236°).

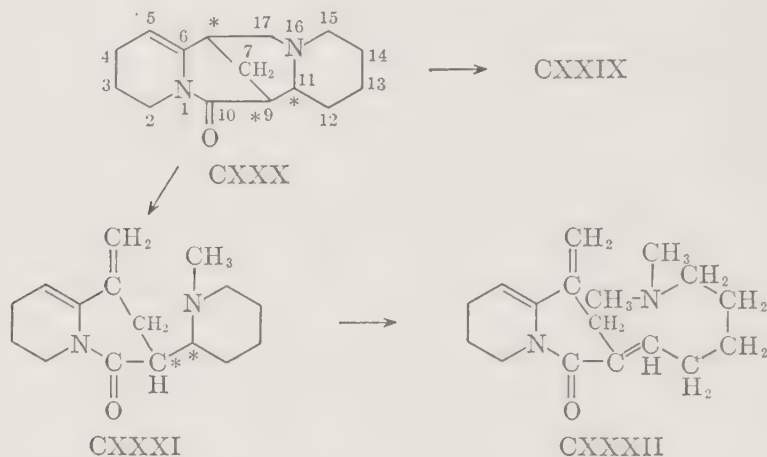
i. Aphylline, $C_{15}H_{24}N_2O$. Anabasine occurs with lupinine in *Anabasis aphylla* (306) and can be separated therefrom by the method of Sadykov (29). Thus, a nicotine alkaloid and a lupin alkaloid have been shown to be coexistent in the same plant. Higher-boiling fractions were also obtained after the separation of the anabasine, and from these fractions two other lupin alkaloids have been isolated and characterized: aphylline, $C_{15}H_{24}N_2O$ and aphyllidine, $C_{15}H_{22}N_2O$. Their interrelation has been established since it has been shown that aphylline (picrolonate, m.p. 233–234° (24); methiodide, m.p. 219–221° (24)) is dihydroaphyllidine. (On this basis, the choice of names of these two alkaloids is unfortunate since the ending “-idine” is usually associated with the more saturated amine.) The hydrogenation of aphyllidine as the hydrochloride with platinum oxide catalyst proceeded slowly at room temperature. When two atoms of hydrogen had been absorbed, the product was isolated as the hydrochloride, $C_{15}H_{24}N_2O \cdot HCl$, and was shown to be identical with aphylline hydrochloride (26). The catalytic hydrogenation of aphyllidine at 80–90° proceeded in a different manner, though presumably through the aphylline, to give $C_{15}H_{26}N_2$. This fully reduced product was isolated as the dipicrate, m.p. 205–206°, which was identical with *d*-sparteine dipicrate. This experiment established the basic ring structure in aphylline as that of sparteine (XCI), and since the presence of a lactam group was realized, Orekhov (28) assigned structure CXXIX to aphylline. It will be remembered that the carbonyl group in isomeric lupanine was assigned to ring A and in isomeric oxysparteine, to ring C. The lactam group in



aphylline differs from those in lupanine and oxysparteine in that it is readily susceptible to hydrolytic cleavage. It differs from that in oxysparteine in its ease of catalytic reduction. Therefore it has been assigned to ring B in aphylline (28). Galinovsky and Stern (188) supported the structure assigned by Orekhov when they found that aphylline in dilute hydrochloric acid underwent hydrogenation over platinum to give *d*-sparteine and that oxysparteine was unchanged under the same conditions. They pointed out that although rings B and C of sparteine are identical structurally they are configurationally different. Hence, the difference in reactivity of a lactam group in B or C is explicable on the basis of the different configurations of the two inner rings of sparteine. The lactam group in aphylline was readily opened by hydrochloric acid hydrolysis

(24). Ethyl and methyl esters of aphyllic acid were prepared: ethyl aphyllate, $C_{17}H_{30}N_2O_2$ (monohydrate, m.p. 76–77°, $[\alpha]_D^{18}$ 25.3° (methanol)); methyl aphyllate, $C_{16}H_{28}N_2O_2$ (monohydrate, m.p. 82–83°). Hydrolysis of either ester yielded aphyllic acid, $C_{15}H_{26}N_2O_2$, m.p. 218–221°. On repeated distillation of the acid, the lactam, $C_{15}H_{24}N_2O$ ($[\alpha]_D^{18}$ 10.1° (methanol)), was reformed and was found to be identical with aphylline. The Hofmann exhaustive methylation of aphylline proceeded normally (25), unlike that of either isomer, lupanine or matrine.

j. Aphyllidine, $C_{15}H_{22}N_2O$. This alkaloid (methiodide, m.p. 225–227° (24); picrolonate, 235–236° (25); perchlorate, 210–212° (26); hydrochloride, 235–237° (26)) has been found with aphylline, its dihydro derivative. Orekhov (28) has assigned the structure CXXX to aphyllidine, wherein the position of the double bond was decided on the basis of Hofmann degradation products (25, 28). The unsaturated character of aphyllidine was indicated by bromine and permanganate tests (26) and



by its catalytic reduction to aphylline (26, 188). The basic ring structure was indicated by the conversion of aphyllidine to *d*-sparteine by electrolytic (26) or prolonged catalytic (26, 188) reduction. The lactam group in aphyllidine was readily opened by treatment with ethanolic hydrochloric acid and subsequent formation of an ethyl ester (picrate, m.p. 208–210°) (28). The dibromo derivative first formed when aphyllidine was treated with bromine was unstable and lost one mole of hydrogen bromide spontaneously, with the formation of a crystalline hydrobromide of a monobromoaphyllidine, $C_{15}H_{21}BrN_2O$, m.p. 150–152° (hydrobromide, m.p. 210–211°; perchlorate, 234–235°) (26). The monobromo derivative was exceptionally stable. The bromine could not be removed by catalytic reduction in acid or alkaline solution, or by treatment with methanolic potassium hydroxide. The Hofmann degradation of bromoaphyllidine

through its methiodide (m.p. 114–120°) led to bromo-*des-N*-methylaphyllidine (perchlorate, m.p. 180–183°), identical with the compound obtained by bromination of *des-N*-methylaphyllidine, the product of the first stage of the Hofmann degradation on aphyllidine methiodide (28). Both the Hofmann degradation and the modified (by hydrogenation at each stage) Hofmann degradation (25, 27) were applied to aphyllidine. The basic nitrogen was lost at the third stage, and by both methods optical activity was lost at the second stage. That is to say, *des-N*-dimethylaphyllidine (b.p. 240–242° (5 mm.); perchlorate, m.p. 180–182°) and dihydro-*des-N*-dimethylaphyllidine (b.p. 218–220° (5 mm.); perchlorate, m.p. 209–210°) had no optical activity whereas their precursors did. In order to account for loss of activity at this stage, Orekhov (28) pointed out that the olefinic bond must be located between C₅ and C₆. In the first stage of the Hofmann degradation, then, fission could occur at C₁₇ or C₁₁ (structure CXXXI would represent the product of first cleavage at C₁₇-N₁₆). In the second stage, fission would occur at C₁₁ or C₁₇ (structure CXXXII would represent the product of the second cleavage, in whichever order the fissions occurred). In order to have lost activity completely, this second product had to have a double bond between C₅ and the otherwise potentially asymmetric C₆. The bond must likewise have been in this position in the starting material, aphyllidine.

k. Monspessulanine, C₁₅H₂₂N₂O. This alkaloid, isolated by White (36), is isomeric with aphyllidine and allied to the lupanine bases in that it contains a tertiary amine group and an amide group. Monoacidic salts were formed with hydrochloric acid (m.p. 244°) and perchloric acid (m.p. 215°) and a monomethiodide (m.p. 249°). Monspessulanine reduced chloroauric acid and potassium permanganate. The presence of a double bond was also indicated by its catalytic reduction to dihydro-monspessulanine, C₁₅H₂₄N₂O (m.p. 99°, [α]_D 10 to 13° (ethanol); perchlorate, m.p. 224°). The dihydro compound has not been identified with any known base (such as lupanine, matrine, aphylline, oxysparteine) of this formula.

l. P1, C₁₅H₂₂N₂O. An alkaloid designated as "P1" (m.p. 126°) was isolated by Marion (18) from *Lupinus macounii*. Analysis was fair for this isomer of aphyllidine and monspessulanine, but insufficient material was available for further purification or characterization.

m. Ammothamnine, C₁₅H₂₄N₂O₃. This isomer of trilupine was isolated by Sadykov and Lazur'evskii (3) from *Ammothamnus lehmanni*. It was optically inactive and was characterized by the picrate, m.p. 212–214°, and hydriodide, m.p. 183–189°. A Zerewitinoff determination indicated the presence of a hydroxyl group, and there apparently was an *N*-methyl group present.

n. Sophoridine, $C_{15}H_{26}N_2O$. Sophoridine has been assigned this molecular formula on the basis of analysis of the alkaloid and its methiodide, m.p. 234–236° (101). The formula is inconsistent, however, with that ($C_{15}H_{26}N_2$) of the compound obtained by electrolytic reduction (99). Sophoridine forms monoacidic salts (aurichloride, m.p. 189–190°; picrolonate, m.p. 226–228°) and contains a lactam group (101). The electrolytic reduction product, $C_{15}H_{26}N_2$, had a higher *levorotation* than *l*-sparteine, $[\alpha]_D - 37.1^\circ$ (ethanol), and differed also from sparteine in that it formed a *dimethiodide* (m.p. >260°) (99). This $C_{15}H_{26}N_2$ base was also different from the isomeric compound obtained on electrolytic reduction of sophocarpine.

o. Virgiline, $C_{16}H_{26}N_2O_2$, was isolated by White (39) from *Virgilia capensis* and was characterized by the formation of a number of derivatives: hydrochloride, m.p. 262°; methiodide, 176°; picrate, 188–189°; *O*-acetyl derivative, 174°. White found that it contained a tertiary amine group, an hydroxyl group, and an inert carbonyl group and suggested that virgiline was probably allied to sparteine, containing in addition a *C*-methyl group.

p. Dilupine, $C_{16}H_{26}N_2O_2$. There is some doubt as to the molecular formula for dilupine, isolated by Couch (44), since it apparently lost one oxygen atom very readily. The methiodide, $C_{16}H_{26}N_2O \cdot CH_3I$, m.p. 253°, was formed with the loss of oxygen, as with trilupine, and Couch therefore suggested that dilupine might be an amine oxide. From the hydrobromide, $C_{15}H_{26}N_2O \cdot HBr$, m.p. 233–234°, was obtained a base different from dilupine, which had analysis compatible with $C_{16}H_{26}N_2O$ and a lower specific rotation, $[\alpha]_D^{25} + 49.8^\circ$ (water). Provisionally, dilupine appears to be the amine oxide of a *C*-methyllypanine (44).

8. ALKALOIDS RELATED TO ANAGYRINE

a. Sophoramine, $C_{15}H_{20}N_2O$. Isomeric with anagyrine, sophoramine (21, 101) showed strong unsaturated character, and the presence of a tertiary amine and a lactam group were indicated. A number of salts were prepared: aurichloride, m.p. 183–184°; hydrochloride, 247–248°; hydriodide, 294–296°; platinichloride (dihydrate), 245–247°; picrate, 229–231°; picrolonate, 173–175°.

b. Thermopsine, $C_{15}H_{20}N_2O$. A second isomer of anagyrine, *l*-thermopsine (4, 21), is not identical with sophoramine, as indicated by its physical constants and those of its derivatives: picrate, m.p. *ca.* 253° (21, 22); perchlorate, 289° (323); platinichloride, 254–256°; hydriodide, 306–308°; methiodide, 241–242°. *d*-Thermopsine has been isolated from one of the *Lupinus* species by Marion, Turcotte, and Ouellet (310), and has been shown to be identical (315) with the alkaloid “hexalupine”

(47). The presence of a tertiary amine group and an indifferent oxygen and nitrogen were indicated. *l*-Thermopsine exhibited unsaturation when treated with permanganate and was readily hydrogenated over platinum oxide in hydrochloric acid solution (21). Four atoms of hydrogen were absorbed to give *l*-tetrahydrothermopsine, $C_{15}H_{24}N_2O$ (m.p. 74–75°, $[\alpha]_D^{26} - 64.3^\circ$ (ethanol); picrate, m.p. 196–198°; perchlorate, m.p. 237° (d.); platinichloride, m.p. 241–242° (21, 323). Further reduction, by the electrolytic method, resulted in the isolation by Orekhov, Gurevich and Okolskaya (307) of an unusual product of apparent composition $C_{15}H_{28}N_2O$. The recognition by Cockburn and Marion (323) that this product had composition and properties suggestive of α -isosparteine hydrate, $C_{15}H_{26}N_2 \cdot H_2O$, furnished an important clue toward their elegant solution of the structural problems presented by thermopsine and its congeners. The findings of Cockburn and Marion (323) are described below.

The infrared absorption spectrum of thermopsine, while different from that of the isomeric alkaloid anagryne, showed striking general similarity and thus provided strong spectroscopic evidence for the presence in thermopsine, as in anagryne (XCIII), of an α -pyridone ring. The position of the infrared carbonyl for thermopsine (1653 cm^{-1}) was practically identical with those for the α -pyridone-type alkaloids: anagryne (1652 cm^{-1}), cytisine (1653 cm^{-1}), and *N*-methyleytisine (1653 cm^{-1}). Furthermore, in tetrahydrothermopsine, the carbonyl peak is shifted to 1613 cm^{-1} , which is close to that for lupanine, an α -piperidone type and the hydrogenation product of anagryne. When thermopsine was hydrogenated over platinum in hydrochloric acid solution, four molecules of hydrogen were absorbed with the formation of a fully reduced compound, $C_{15}H_{26}N_2$, isolated as the hydrate. This hydrate was identical in its properties with the hydrate of *l*- α -isosparteine obtained by Winterfeld and Rauch (267) (see above), and a direct comparison of the two products definitely established the thermopsine reduction product as α -isosparteine. *d*-Thermopsine yielded *l*- α -isosparteine and *l*-thermopsine yielded *d*- α -isosparteine (323). The active thermopsines are thus diastereoisomers of *l*-anagryne (all represented by the non-stereospecific formula XCIII), and *l*-tetrahydrothermopsine is the enantiomorph of *d*- α -isolupanine (XCIV) (310).

c. Homothermopsine, $C_{17}H_{24}N_2O$. This alkaloid was obtained (4), along with thermopsine, anagryne, *d*-sparteine, and methyleytisine in *Thermopsis lanceolata*. The physical properties, as with the other alkaloids, are given in Table 1.

d. Baptifoline, $C_{15}H_{20}N_2O_2$. This alkaloid, also referred to as 'P3' (8), was characterized by its derivatives: perchlorate, m.p. 289.5°,

$[\alpha]_D^{16} - 89.05^\circ$ (water); hydrochloride, m.p. $322-323^\circ$; picrate (with 1 CH_3OH), m.p. 145° with gas evolution, followed by resolidification and melting at 256° (7).

e. *Rhombifoline*, $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_2$. This amorphous alkaloid formed crystalline salts: perchlorate, m.p. 242° ; picrate, m.p. 207° (22).

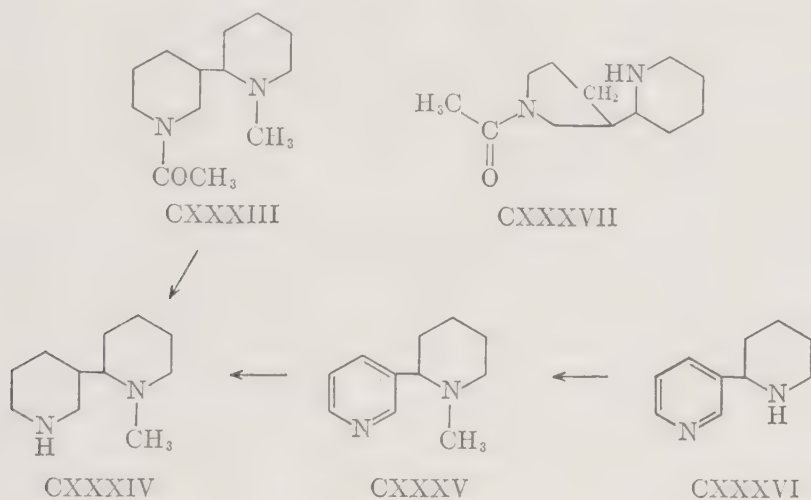
f. $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_5$. Only a few milligrams of this alkaloid, m.p. 170° , have been obtained (23).

9. ALKALOIDS WITH A PIPERIDINE NUCLEUS

Compounds with a pyridine or piperidine nucleus form the bridge between the lupin alkaloids and the nicotine alkaloids. The compound 3-methoxypyridine has been identified by Manske (87) as occurring in *Thermopsis rhombifolia* along with the lupin alkaloids: thermopsine, cytisine, methylcytisine, and anagryrine. The same compound was also found along with nicotine in *Equisetum arvense* by Manske and Marion (86). Another compound, an alkaloid closely resembling the nicotine alkaloid anabasine, has been found in the Leguminosae, namely, ammodendrine, obtained from *Ammodendron conollyi*.

Ammodendrine, $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}$. This alkaloid was characterized by Orekhov, Proskurnina, and Lazur'evskii (2) as a monoacidic secondary base (hydriodide, m.p. $218-220^\circ$; perchlorate, $199-200^\circ$; *N*-methylammodendrine, $65-66^\circ$; *N*-methyl hydriodide, $183-185^\circ$; *N*-methyl methiodide, $163-165^\circ$). It was also realized that the non-basic nitrogen was part of an amide grouping. The structural investigation of ammodendrine was attacked successfully by Orekhov and Proskurnina (308). The presence of an acetyl group in ammodendrine, $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}$, was indicated by cleavage of the alkaloid with methanolic potassium hydroxide. The products were acetic acid, identified as its silver salt, and a resinous base, $\text{C}_{10}\text{H}_{18}\text{N}_2$, which could not be converted to crystalline derivatives. The presence of a double bond in ammodendrine was indicated by catalytic reduction. Dihydroammodendrine, $\text{C}_{12}\text{H}_{22}\text{N}_2\text{O}$, was obtained, which underwent hydrolysis with methanolic potassium hydroxide to give acetic acid and a crystalline base $\text{C}_{10}\text{H}_{20}\text{N}_2$, m.p. $65-67^\circ$ (dihydrochloride, m.p. $>300^\circ$; dihydrobromide, $>300^\circ$; picrate, $225-226^\circ$; dinitroso derivative, $86-87^\circ$). In order to establish the ring system present in $\text{C}_{10}\text{H}_{20}\text{N}_2$ (and accordingly in ammodendrine), it was subjected to dehydrogenation by heating in a sealed tube with silver acetate and acetic acid at 180° . The dehydrogenation product, $\text{C}_{10}\text{H}_8\text{N}_2$, proved to be a dipyridyl, and from the melting points of various derivatives (monopierate, m.p. $151-152^\circ$; dipierate, $164-165^\circ$; monomethiodide, $164-165^\circ$), was shown to be the α,β -isomer. The structure of the $\text{C}_{10}\text{H}_{20}\text{N}_2$ hydrolysis product of dihydroammodendrine was therefore α,β -dipiperidyl.

To fix the position of the acetyl group in dihydroammodendrine, and in ammodendrine itself, *N*-methyldihydroammodendrine was prepared (methiodide, m.p. 177–180°) and was hydrolyzed to an *N*-methyl- α,β -dipiperidyl. This was identical with the product (CXXXIV) obtained from *dl*-anabasine, a nicotine alkaloid of known structure (CXXXVI), by methylation (CXXXV) followed by reduction of the pyridine ring. *N*-Methyldihydroammodendrine is therefore represented by structure CXXXIII, and dihydroammodendrine by structure CXXXVII, which has been written in such a way that the relation to the



other lupin alkaloids is apparent. The position of the double bond in ammodendrine remains in doubt.

10. MISCELLANEOUS LUPIN ALKALOIDS

a. Calycotamine, $C_{11}H_{15(17)}NO_3$. Traces of this alkalo'd have been found by White (30) along with calycotomine (see below). The assignment of molecular formula was based on analysis of the hydrochloride, m.p. 206°, $[\alpha]_D$ 20° (water), which was probably not entirely free from calycotomine hydrochloride. Calcotamine was found to contain two methoxyl groups.

b. d-Calycotomine, $C_{12}H_{17}NO_3$. Calycotomine has been found in both *dextrorotatory* and *racemic* forms. *d*-Calycotomine has been characterized by the formation of a number of derivatives: hydrochloride, m.p. 193°, $[\alpha]_D$ 15° (water); picrate, 163–166° (d.); perchlorate, 176–177°; mercurichloride, 118–119° (30). A secondary amine function was indicated by the formation of a nitrosamine and of an *N*-methyl derivative by treatment with formaldehyde—formic acid or methyl iodide (hydrochloride, $C_{13}H_{20}ClNO_3$, m.p. 216°; hydriodide, m.p. 228–229°). A dibenzoyl derivative was formed (m.p. 120–122°) and a Zerewitinoff deter-

mination showed two active hydrogens. These findings showed the presence of an hydroxyl group, which was indicated as aliphatic by the lack of any phenolic color reactions. The base was also shown to possess two methoxyl groups, but no *C*-methyl or *N*-methyl group. Demethylation afforded a phenolic material, which established the presence of a benzene ring—the first to be found in any of the lupin alkaloids. *d*-Calycotomine gave no indole color reactions and was stable to hydrolytic reagents and catalytic reduction. Oxidation by permanganate gave a solid, m.p. 316°, whose analysis indicated the molecular formula $C_{11}H_{11}NO_4$.

c. dl-Calycotomine, $C_{12}H_{17}NO_3$. The racemic alkaloid, which was also isolated by White (30, 31), formed a perchlorate, m.p. 172°, and a hydrochloride, m.p. 193°.

d. Pentalupine, $C_{16}H_{30}N_2O$. No derivatives have been reported for this alkaloid isolated by Couch (78).

e. Sophochrysine, $C_{13-15}H_{21-19}N_3O_2$. The formula for sophochrysine (picrate, m.p. >360°; picrolonate, 265.5–267°; aurichloride, 190–192°), obtained by Briggs and his coworkers (20, 40, 83, 84), is uncertain.

f. P2, $C_{11}H_{18}N_2O$. A perchlorate (m.p. 198°) and a picrate (m.p. 241° after sintering at 185°) of this alkaloid were made (8, 32).

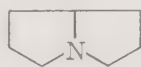
g. P4. A perchlorate (m.p. 286°) of the alkaloid so designated has been prepared.

h. Base E. An aurichloride (d.p. 211°) of the alkaloid designated as Base E was made by Briggs and Ricketts (40).

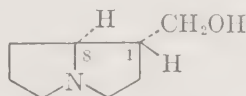
i. Sarothamnine, $C_{30}H_{50}N_4$. This alkaloid, originally isolated by Valeur (98) and assigned the formula $C_{15}H_{24}N_2$, has been reinvestigated by Delaby, Baronnet, and Guy (314) and is now considered to be a bispar-teine-type alkaloid. Evidence presented for a $C_{30}H_{50}N_4$ saturated structure includes the following facts: (a) sarothamnine fails to absorb hydrogen in the manner characteristic of ethylenic unsaturation, (b) the infrared absorption spectrum is similar to that for sparteine and indicates the lack of $C=C$, $C=N$, $-CH_3$, and $=NH$ groups in the alkaloid, (c) a molecular weight determination by the ebullioscopic method gave a value of 460 ± 4 (theor. 466.73), (d) the alkaloid was not identical with the spartyrine, $C_{15}H_{24}N_2$, of Willstätter and Marx (263), and (e) the alkaloid added solvents of crystallization in equimolar proportion: $C_{30}H_{50}N_4 \cdot CHCl_3$, m.p. 131–132° (d.); $C_{30}H_{50}N_4 \cdot O(CH_2CH_2)_2O$, m.p. 128–129° (d.); $C_{30}H_{50}N_4 \cdot C_2H_5OH$, m.p. 110–115° (d.) (314).

j. Laburnine, $C_8H_{15}NO$. Cytisine was the only alkaloid isolated from the seeds of *Cytisus laburnum* (35), until Galinovsky, Goldberger, and Pöhm (313) found an accompanying alkaloid, laburnine, $C_8H_{15}NO$, in 1.5% yield. The alkaloid, which is a colorless oil, forms a picrate, m.p.

172–173°; picrolonate, m.p. 181–182°; methiodide, m.p. 307–309°. A Zerewitinoff determination indicated the presence of one active hydrogen which had to be part of an OH-group due to the methiodide formation. Hofmann degradation on laburnine methiodide required three operations to obtain a nitrogen-free product, so that the nitrogen must be tertiary and common to two rings. The hydroxyl was established as primary by chromic acid oxidation of laburnine to an amino acid, and the ring structure was established by the decarboxylation of this amino acid to pyrrolizidine (CXXXVIII). The $C_7H_{13}N$ base (CXXXVIII) was identified by direct comparison with an authentic sample of pyrrolizidine.



CXXXVIII



CXXXIX

The most unusual feature of the alkaloid laburnine is that it belongs to the lupin alkaloid family due to its source and to the *Senecio* alkaloid family (324) due to its constitution as a derivative of pyrrolizidine (CXXXVIII) rather than quinolizidine (I). The preferred position of attachment of the CH_2OH -group on the pyrrolizidine nucleus in laburnine is C-1 (CXXXIX), since Galinovsky and his coworkers (313) pointed out that Men'shikov's trachelanthamidine (known to be a 1-hydroxymethylpyrrolizidine) (325) and their laburnine were probably optical antipodes. The properties of the derivatives of the two compounds are similar and the optical rotations are approximately equal and opposite.

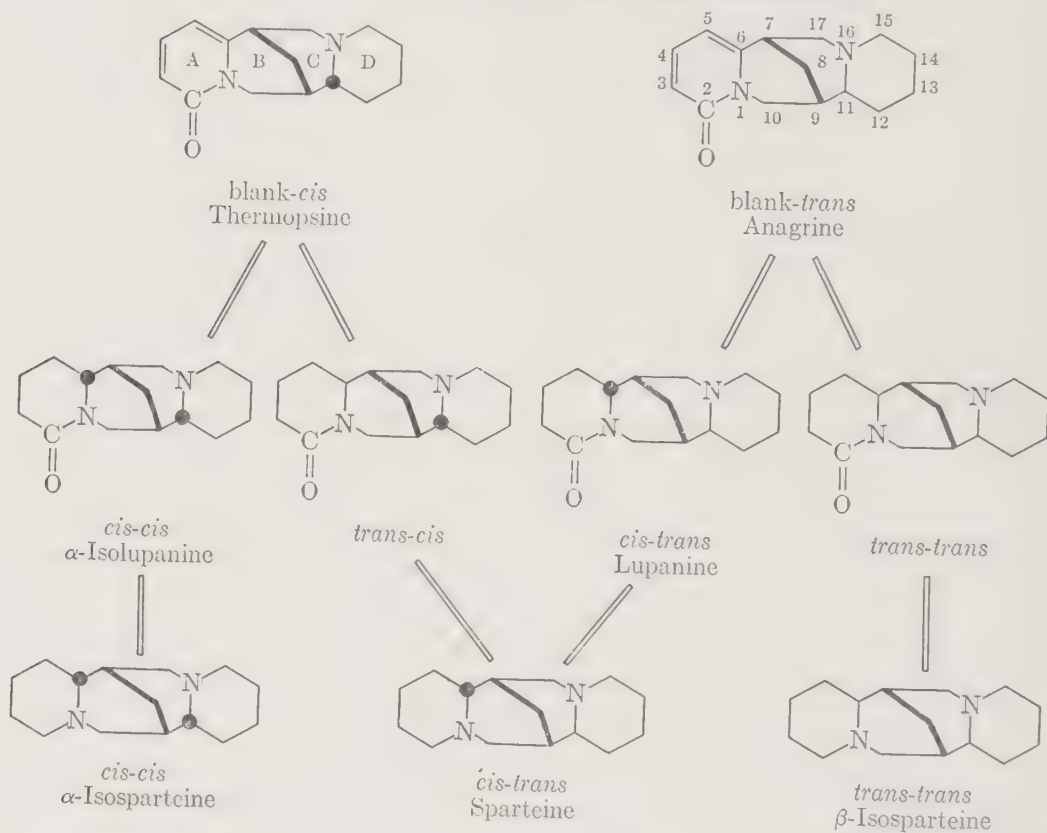
Another unusual feature of laburnine is that it was synthesized prior to the knowledge of its natural occurrence as an alkaloid. A 1-hydroxymethylpyrrolizidine was synthesized by Leonard and Felley (326) which corresponded to *dl*-trachelanthamidine, or *dl*-laburnine. According to these workers the stereochemical structure of (*d*-)laburnine can also be decided, as represented in CXXXIX, as one of the enantiomorphs with the C_1-CH_2OH *cis* to the C_8 -hydrogen.

IV. Stereochemistry of the C_{15} -Lupin Alkaloids

On the basis of evidence and knowledge presently accumulated, it has been possible to assign absolute stereochemical structures to the members of the C_{15} family of lupin alkaloids. The arguments of Marion and Leonard (320) rest upon (a) the structural similarity but configurational difference between rings B and C' in sparteine and its derivatives (278), (b) the study of accurate scale molecular models, and (c) the recognized surface nature of the catalytic hydrogenation process (327), as applied to certain of the alkaloid interconversions. Consistent with

all of the existing structural and stereochemical data (320) is the assignment of the structures in Chart 1 (The heavy line between C₇ and C₉ indicates the methylene group to be above the plane of the page and a heavy dot at C₆ and/or C₁₁ indicates a hydrogen atom above the plane of the page.) for thermopsine, α -isolupanine, α -isosparteine, anagryne, lupanine, and sparteine, and the predicted β -isosparteine. Only one enantiomorphous form of each racemate has been indicated throughout.

CHART 1
STEREOCHEMICAL FAMILY—C₁₅ LUPIN ALKALOIDS



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CHAPTER 20

The Imidazole Alkaloids

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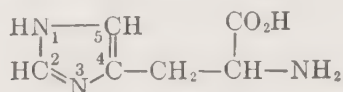
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	<i>Page</i>
I. Bases Related to Histidine.	202
1. Occurrence and Isolation	202
2. Physical, Chemical and Physiological Properties: Structural Elucidation	203
a. Histamine and Dimethylhistamine.	203
b. Hereynine	203
c. Ergothioneine.	203
3. Table of Physical Constants.	205
II The Jaborandi Alkaloids	206
Introduction.	206
III. Pilocarpine and Isopilocarpine.	207
1. Occurrence and Isolation	207
2. Physical and Physico-chemical Properties.	209
3. Precipitation and Color Reactions: Estimation.	210
4. Physiological Properties	213
5. The Interconversion of Pilocarpine and Isopilocarpine	213
6. Determination of Structure.	214
a. Functional Groups	214
b. Oxidation with Permanganate: Isopilopic and Homoisopilopic Acids	216
c. Effect of Other Oxidizing Agents	219
d. Alkaline Degradation: the Imidazole Nucleus.	220
e. Relation of Pilocarpine to Isopilocarpine.	221
7. Substitution Products and Other Derivatives	222
a. Halogenation.	222
b. Nitration.	224
c. Metapilocarpine.	224
8. Synthesis of Pilocarpine and Isopilocarpine	225
IV. Pilocarpidine.	228
1. Occurrence and Isolation	228
2. Physical, Chemical and Physiological Properties.	229
3. Structural Investigation	230
V. Pilosine.	230
1. Occurrence and Isolation	230
2. Physical, Chemical and Physiological Properties.	230
3. Structural Investigation	231
4. Synthesis of Pilosinine	232
VI. Tables of Physical Constants of the Jaborandi Alkaloids, Their Derivatives and Degradation Products.	233
VII. References.	242

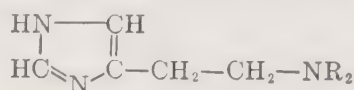
I. Bases Related to Histidine

1. OCCURRENCE AND ISOLATION

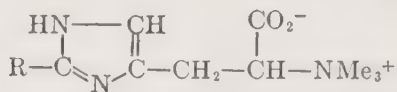
In view of the close structural relationship existing between the alkaloids and many of the natural amino acids, it is surprising that only very few alkaloids contain the imidazole nucleus occurring in the amino acid histidine (I). Apart from the purine bases, which are probably not genetically related to histidine, the only representatives of this group so far discovered in the higher plants are the alkaloids of Jaborandi. Certain fungi, however, contain a few bases very closely related structurally to histidine. Histamine (II) occurs in ergot (1), and a dimethylhistamine,



I



II, R = H
III, R = CH₃



IV, R = H
V, R = SH

probably III, has been isolated from the sponge, *Geodia gigas* (2). Trimethylhistidine betaine (IV) and its 2-thiol derivative (V) have also been isolated from fungal sources. The former was first isolated from a commercial extract of mushrooms ("Hercynia" of Krewel and Co.) by F. Kutscher (3), who gave it the name *hercynine*, and it was subsequently found in *Boletus edulis* Bull. by C. Reuter (4). *Ergothioneine* (V) was isolated from ergot by C. Tanret (5), and it was extensively investigated by G. Barger and A. J. Ewins (6). It has also been isolated from blood (7, 8).

Ergot is extracted with 90% alcohol, and the extract is concentrated, filtered to remove resin and tar, and treated with 20% sulfuric acid to remove coloring matter and ergotinine. The sulfuric acid is removed by means of barium hydroxide, and the solution is further purified by treatment with basic lead acetate, filtration, and removal of the lead with hydrogen sulfide. The solution is made alkaline, exhaustively extracted with chloroform to free it completely from alkaloids, acidified with acetic acid and precipitated with warm 8% mercuric chloride solution. The washed precipitate is suspended in water and decomposed with hydrogen sulfide, and the filtrate from the mercuric sulfide is concentrated to a sirup. The hydrochloride thus obtained is washed with alcohol and crystallized from water. From 1 kg. of ergot about 1 g. of the hydrochloride is obtained. The free base is isolated by dissolving the hydrochloride in a little water, adding a small excess of calcium carbonate, boiling, and filtering. On cooling the ergothioneine separates; a further quantity is obtained from the mother liquor by concentration and addition of 95% alcohol. The product is recrystallized from 60% alcohol (5).

2. PHYSICAL, CHEMICAL AND PHYSIOLOGICAL PROPERTIES: STRUCTURAL ELUCIDATION

a. Histamine and Dimethylhistamine. Since histamine occurs mainly in animal organisms and is of immense physiological importance, detailed accounts of its chemistry and physiology are available elsewhere (9) and it will not be discussed here. The identity of the histamine isolated from ergot was established by direct comparison with material obtained by the fermentative decarboxylation of histidine (10) and by the agreement of its properties with those recorded for a synthetic specimen (11).

The structure of the dimethylhistamine from *Geodia gigas* has not been conclusively proved, but from its molecular formula, $C_7H_{13}N_3$, its general properties and its ability to give a red color with diazobenzene-*p*-sulfonic acid (see below) it is probably III (2).

b. Hercynine. Hercynine is an optically active diacidic base, its solution in excess of dilute hydrochloric acid having $[\alpha]_D + 41.1^\circ$ (12), $+46.5^\circ$ ($c = 0.39$) (6b). It has been isolated only in the form of its salts. Its molecular formula, $C_9H_{15}O_2N_3$, corresponds to that of a trimethylhistidine, and it gives an intense red color with Pauly's histidine reagent (13) (diazobenzene-*p*-sulfonic acid), characteristic of imidazoles containing a free imino group. Kutscher therefore proposed the structure IV for hercynine, and its correctness was subsequently established by synthesis (14). Treatment of histidine with silver nitrite and concentrated hydrochloric acid yielded 1-chloro-2-(4-imidazolyl)propionic acid (I, Cl for NH_2), which was converted into IV by reaction with trimethylamine.

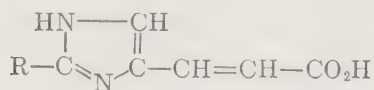
Histidine hydrochloride (2 g.) is suspended in concentrated hydrochloric acid and slowly treated with silver nitrite (3 g.). After removal of excess nitrous acid and silver chloride, the liquid is concentrated to a sirup, which is taken up in alcohol, treated with an excess of alcoholic trimethylamine solution, and kept at 80° for 8 hours. After removal of the alcohol the product is precipitated with phosphotungstic acid. The phosphotungstate is decomposed with barium hydroxide in the usual manner, and the solution of the base thus obtained is strongly concentrated to remove trimethylamine, treated with hydrochloric acid, and the resulting chloride is taken up in alcohol and precipitated with chloroplatinic acid. It is finally converted into the chloroaurate, m.p. 183° with decomposition (14).

The validity of the formulation IV was further confirmed by the preparation of a substance identical with hercynine by the desulfurization of ergothioneine (see below).

c. Ergothioneine. Ergothioneine is a crystalline, optically active substance ($[\alpha]_D = +110^\circ$), nonvolatile and of high melting point. Its ultraviolet absorption shows a maximum at 2580 Å. (14a). It is readily soluble in hot water and moderately so in cold. It is very sparingly soluble in methanol, ethanol, or acetone, and insoluble in ether, chloro-

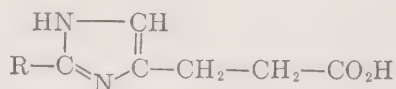
form, or benzene. Although it forms a series of crystalline salts, it is a very weak monoacidic base, its salts with mineral acids behaving on titration as strong acids (5). The base and some of its salts have been examined crystallographically (5c).

Ergothioneine is precipitated from acid solution by mercuric chloride, potassium mercuric iodide, or potassium periodide, but not by picric or tannic acids. The hydrochloride gives with silver nitrate a complex silver salt, $2C_9H_{15}O_2N_3S \cdot 2AgCl \cdot Ag_2O$. On warming with chloroform and alkali a solution of ergothioneine becomes green, changing to blue on neutralization (5). With diazobenzene-*p*-sulfonic acid it gives an intense red coloration (6). Methods for the determination of ergothioneine have been described (14b). Ergothioneine, like other betaines, has no appreciable physiological activity (6, 15); the reported antithyroid activity (15a) is probably not significant (15b).



VI, R = SH

VII, R = H



VIII, R = H

IX, R = SH

On the basis of its molecular formula, $C_9H_{15}O_2N_3S$, its ability to form a silver salt and a mercurichloride, and its reaction with diazobenzene-sulfonic acid, Barger and Ewins (6) concluded that ergothioneine contained an imidazole ring and that it was probably a betaine related to histidine. This hypothesis was readily substantiated by degradation. On boiling with 50% aqueous potassium hydroxide, trimethylamine is evolved, and the base is converted into a yellow acid, $C_6H_6O_2N_2S$ (VI), which is desulfurized by boiling dilute nitric acid to imidazole-4(5)-acrylic acid (*urocanic acid*) (VII). On reduction with sodium and alcohol this yields imidazole-4(5)-propionic acid (VIII), the identity of both these substances being established by comparison with synthetic specimens.

The position of the thiol group is not established by the foregoing degradation, but may be inferred by the resemblance in the behavior of ergothioneine to that of known 2-thiolimidazoles (6). Thus, the sulfur is not removed by concentrated alkali, but ferric chloride or bromine water oxidize it quantitatively to sulfuric acid; the second product obtained by the action of ferric chloride was identified as trimethylhistidine betaine (IV) by direct comparison (7, 12) with specimens obtained from *Boletus edulis* (4) and synthetically (14). The feebly basic character of ergothioneine, which contrasts markedly with that of hercynine, is a further indication of the nuclear attachment of the thiol group. That this group occupies the 2-position was also strongly indicated by its color reaction with diazobenzenesulfonic acid under specified conditions (8b), and was

confirmed by S. Akabori (16), who identified the sodium amalgam reduction product of (VI) with a synthetic specimen of 2-thiolimidazole-4(5)-propionic acid (IX).

Synthetic confirmation of the structure of ergothioneine has been obtained by H. Heath, A. Lawson and C. Rimington (14a). 2-Thiol-histidine, synthesized by the method of Ashley and Harington (16a), was converted into its *S*-carbethoxy derivative by treatment with ethyl chloroformate. Methylation of this product with methyl iodide and silver oxide gave the silver complex of trimethyl-2-carbethoxythiol-histidine betaine, from which the protecting carbethoxy group was removed by boiling 3 *N* hydrochloric acid. Some earlier, unsuccessful attempts to achieve the synthesis of ergothioneine have been recorded (17).

3. TABLE OF PHYSICAL CONSTANTS

TABLE 1

Compound	M.p., °C.	Crystal form	References
Dimethylhistamine Aurichloride	198		2
Ergothioneine (+2H ₂ O)	ca. 290 (dec)	Colorless lamellae, monoclinic (H ₂ O)	5
Hydriodide (+2H ₂ O)	ca. 100 (dec)	Orthorhombic (H ₂ O)	5
Hydrochloride (+2H ₂ O)	250	Rhombic crystals	5
Mercurichloride (B·HCl·HgCl ₂)		Needles (H ₂ O)	5
Phosphate (B·H ₃ PO ₄)			5
Sulphate (B ₂ ·H ₂ SO ₄ ·2H ₂ O)	ca. 265 (dec)		5
Hercynine			
Aurichloride (B·2HAuCl ₄)	183	Orange-yellow spears (dil. HCl)	4, 14, 6b
Nitrate		Rhombic plates	4
Picrate (mono) (+H ₂ O)	201	Fine, soft needles (H ₂ O)	6
(di) (+2H ₂ O)	123	Flat prisms or long plates (H ₂ O)	6, 11
(anhydr.)	212–213		6b, 11
Picrolonate	229–230	Long thin orange-yellow needles	6a
Imidazole-4-acrylic acid	235–236	Crystals (acetone-H ₂ O)	6a
Nitrate	198 (expl.)		6a
Phosphotungstate		Small rectangular plates (acetone-H ₂ O)	6a
Picrate	213–214	Golden yellow prisms	6a
Imidazole-4-propionic acid	202		6a
2-Thiolimidazole-4-acrylic acid	>275	Small prisms (by acidification of dil. solution of sodium salt)	6a
2-Thiolimidazole-4-propionic acid (+H ₂ O)	205–206.5	Colorless needles (H ₂ O)	16

II. The Jaborandi Alkaloids

INTRODUCTION

The name "Jaborandi" has been applied to a number of closely related South American plants of the order *Rutaceae*, which have aroused great interest because of their valuable pharmacological properties. The drug was first sent to Europe from Pernambuco by a Dr. Coutinho in 1874, and the botanical source of most of the earlier samples was subse-

TABLE 2
ALKALOID CONTENT OF VARIOUS *Pilocarpus* SPECIES

Botanical name	Commercial name or source	Alkaloids present	Percentage total alkaloid (on dry wt.)	Percentage pilocarpine isolated as nitrate ^a	References
<i>P. jaborandi</i>	Pernambuco jaborandi	Pilocarpine	0.72	0.67 (a)	80
		Isopilocarpine		0.5-0.8	19
		Pilocarpidine			
<i>P. pennatifolius</i>	Paraguay jaborandi	Pilocarpine Isopilocarpine	>0.4	0.2-0.4	19, 81
<i>P. pennatifolius</i>	Sicily			0.05 ^b	82
				0.002 ^c	82
<i>P. pennatifolius</i>	Abkhaziya		0.22-0.25		83
<i>P. microphyllus</i>	Maranhão jaborandi	Pilocarpine	0.84	0.45 (b)	80
		Isopilocarpine	0.8	0.16-0.19	19
		Pilosine		0.99	84
			0.76-0.78		85
			0.7 (leaves)		86
			0.5 (stalk)		86
			0.31 (small leaves)		87
<i>P. trachylophus</i> Holmes	Ceará jaborandi	Not known	0.4		80
<i>P. racemosus</i> Vahl.	Guadeloupe jaborandi	Pilocarpine	0.6	0.3 (c)	88
				0.12 (d)	43
			1.0	0.6	20
			0.34		20
<i>P. heterophyllus</i> Griseb.	Barquisimento (Venezuela)	Pilocarpine	0.25	0.04	89
<i>P. spicatus</i>	Aracati jaborandi	"ψ-Pilocarpine"	0.16		80
		"ψ-Jaborine"	0.1		18
		Pilocarpine (?)	0.38	0.26 (?)	18

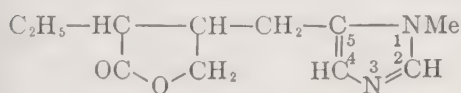
^a In many cases, the product isolated is not pure pilocarpine nitrate, as is evidenced by the recorded melting points: the m.p. of the pure salt is 178°. (a) m.p. 161°. (b) m.p. 160°. (c) m.p. 155°. (d) m.p. 178°.

^b Fresh leaves.

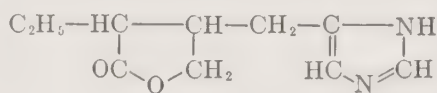
^c Dry leaves.

quently shown to be *Pilocarpus jaborandi* Holmes (18–21) although *P. pennatifolius* Lem. was also used (21). Between 1893 and 1896, however, these two sources of the drug were gradually replaced by *P. microphyllus* Stapf, which remains the most important source today. The leaves of various other species have appeared on the market at different times, and Table 2 summarizes the available data regarding the alkaloidal content of the several varieties of Jaborandi.

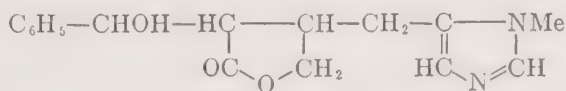
Four well-defined alkaloids, pilocarpine (I), its stereoisomer isopilocarpine, pilocarpidine (II) and pilosine (III), have been isolated from jaborandi and their structures have been fully elucidated. In addition, A. Petit and M. Polonovski (49) reported the isolation from *P. spicatus* A. St. Hil. of two further alkaloids, ψ -pilocarpine and ψ -jaborine; both were amorphous, optically inactive bases which were not completely characterized. D. Parodi (22) described the isolation of a weak base, "jaborandine," $C_{20}H_{12}O_6N_2$ (?), melting point 110° , from a sample of "Paraguay jaborandi" derived from a *Piper* species, and E. Harnack and H. Meyer (23) reported the existence in commercial jaborandi of a base "jaborine"; neither of these substances has been found by subsequent investigators. H. A. D. Jowett (28) showed that a sample of "jaborine" obtained from Merck was a mixture containing isopilocarpine, pilocarpidine, and possibly some pilocarpine.



I



II



III

III. Pilocarpine and Isopilocarpine

1. OCCURRENCE AND ISOLATION

The presence of alkaloids in jaborandi was first reported by M. Byasson (73) and the principal alkaloid, pilocarpine, was isolated independently by A. W. Gerrard (74–77) and E. Hardy (78) both of whom characterized it by the preparation of several crystalline salts. A. Petit and M. Polonovski (50) showed the presence of a second alkaloid, isomeric with pilocarpine; although pilocarpine is easily converted into the new base under a variety of conditions (see Section 5), they maintained that it also occurs in the leaves and is not purely an artifact formed during the isolation processes. Jowett (28) named this base isopilo-

carpine and confirmed the conclusions of the French investigators. He also showed that the alkaloid was present in commercial pilocarpine nitrate. The amount of isopilocarpine present can be estimated by the specific rotation of the mixture (50) and according to the variety of jaborandi, it may constitute from 5 to 75% of the total alkaloids. The proportions of the two alkaloids also varies in different parts of the plant, the twigs in general containing a higher proportion of isopilocarpine than the leaves (50). There can be no doubt that the presence of these two isomeric alkaloids in jaborandi, and their ready interconversion, accounts for many of the discrepancies apparent in the results of the earlier workers.

No detailed directions for the isolation of the jaborandi alkaloids on the laboratory scale appear to have been published, but F. Chemnitius (81) describes a typical large scale extraction procedure.

The drug (500 kg.) is thoroughly broken up in a disintegrator and packed into a copper vessel with a sieve bottom. A layer of woodwool on the sieve retains the particles of leaf, and further layers of this material are introduced at intervals to increase the porosity of the mass. The alkaloids are extracted exhaustively with hot 80% alcohol (denatured with 1.5% carbon tetrachloride), four to five extractions usually sufficing; the completeness of the extraction is checked with Mayer's reagent. The main alcoholic extract is freed from alcohol by distillation and the residue is stirred vigorously while still hot with paraffin wax (m.p. 40–42°, 10 kg.). When cold, the solid wax is lifted out and extracted four times with twice its volume of hot water. The paraffin is again separated, and the aqueous solution is combined with the main bulk of extract and treated with 10% aqueous sodium carbonate solution, with vigorous stirring. A dark resinous mass which precipitates is rejected, and the clear brown solution is extracted thrice with chloroform. After drying the extract over potassium carbonate, the chloroform is distilled and the crude residue is dissolved in two parts of 99% alcohol. Pure concentrated nitric acid is added with stirring and efficient cooling until the solution is slightly acid. A little ether is added to initiate the precipitation of the nitrate, which is complete after 24 hours in the ice-chest. The nitrate is collected, washed with cold 99% alcohol until the washings are colorless, then with ether, and recrystallized thrice from 90% alcohol, using charcoal, to give colorless pilocarpine nitrate, m.p. 175°. This is dissolved in distilled water, made strongly alkaline with ammonia and the free base extracted with three to four portions of chloroform. The dried extract is evaporated to leave hygroscopic needles of pure pilocarpine, m.p. 34°.

An improvement in the extraction procedure (90) involves adding an acidic reagent to the leaves and extracting with benzene to remove fatty materials. The leaves are then rendered alkaline and the alkaloids are extracted with alcohol or benzene and purified through their salts. Other procedures have been outlined (78, 91).

The separation of isopilocarpine from pilocarpine is often very difficult since mixtures containing between 50% and 66% of isopilocarpine yield nitrates that on recrystallization give products of constant melting

point (28, 80). The two hydrochlorides behave similarly (28). In order to obtain pure isopilocarpine from such a mixture, Jowett (28) crystallized successively the nitrates, hydrochlorides, hydrobromides, and again the nitrates, some forty crystallizations being required in all.

2. PHYSICAL AND PHYSICO-CHEMICAL PROPERTIES

Pilocarpine and isopilocarpine are usually obtained as colorless, viscous oils, but both have been crystallized as low-melting, hygroscopic solids (39, 50). Pilocarpine is triboluminescent (93). It is readily soluble in water, alcohol, and chloroform (28, 78, 50), fairly soluble in benzene (50), and almost insoluble in ether or light petroleum (28). Isopilocarpine is very similar in its solubility (28, 50). Pilocarpine base, in alcoholic solution, shows an absorption maximum of low intensity at 2630 Å (94); in pilocarpine salicylate the bands of salicylic acid dominate the spectrum. The absorption in the ultraviolet of solutions of the nitrates of the alkaloids, recorded by Jowett (33), appear to be due solely to the nitrate ion. The infrared absorption spectra of pilocarpine and its hydrochloride have been examined (95).

Both alkaloids are optically active, and their specific rotations are lowered by the addition of alkali (see Table 3), due to the opening of the lactone ring. The rotation of pilocarpine also falls on standing in aqueous solution. The salts of the alkaloids are all dextrorotatory.

TABLE 3

EFFECT OF ALKALI ON THE SPECIFIC ROTATION OF PILOCARPINE AND ISOPILOCARPINE

Alkaloid	Molar proportion of alkali	Concentration of alkaloid	Solvent	$[\alpha]_D$	Refer- ences
Pilocarpine	None	2.0	Water	+106°	50
		1.06 → 19.8	Water	+100.5°	28
Pilocarpine	0.25 NaOH	5.95	Water	+ 85.4°	28
Pilocarpine	0.5 NaOH	5.95	Water	+ 62.47°	28
Pilocarpine	1.0 NaOH	5.95	Water	+ 32.21°	28
Pilocarpine	4.0 NaOH	2.97	Water	+ 33.62°	28
Pilocarpine	1.0 or more NaOH, heated	2.83	Water	+ 21.15°	28
		3.84	Water	+ 23.8°	50
		2.09	Ethanol	+ 25.5°	56
Pilocarpine	None; solution kept for 3 weeks	7.09	Water	+ 77.53°	28
Isopilocarpine	None	6.56 → 11.65	Water	+ 42.8°	28
		2.0	Water	+ 50°	50
Isopilocarpine	1.0 or more NaOH		Water	± 0°	28
			Water	— 3°	50, 56
Isopilocarpine	Excess NaOEt	1.30	Ethanol	+ 7.2°	56

Both pilocarpine and isopilocarpine behave as monoacidic bases, and a large number of crystalline salts of the two alkaloids have been described (see Section VI). By conductimetric (96) and potentiometric (97) titration, the first dissociation constant of pilocarpine was found to be 1×10^{-7} and 1.07×10^{-7} respectively; that of isopilocarpine is 0.68×10^{-7} (97). By the indicator method, J. M. Kolthoff (98) estimates the first and second dissociation constants of pilocarpine to be 7×10^{-8} and 2.7×10^{-13} respectively. When pilocarpine is dissolved in excess of acid and back titrated with sodium hydroxide, a sharp break in the titration curve is observed at pH 4.31 (99). The pH of a solution of pilocarpine hydrochloride, measured electrometrically, is 4.44 at 18° (100). The influence of pilocarpine on the electrocapillarity curve of mercury has been determined by M. Gouy (101).

3. PRECIPITATION AND COLOR REACTIONS: ESTIMATION

Pilocarpine gives precipitates with silicotungstic (102, 103, 104) phosphotungstic, (105) phosphomolybdic (91), hydroferri- and hydroferrocyanic acids (106), with auric (107, 108, 109, 28, 50) and platinic (28, 36, 51, 107) halides, and with Dragendorff's (110), Wagner's (107, 111), and Mayer's (112), reagents. Complex salts recommended for its identification include the aurichloride (107), iodoargentate (113), iodo-stibnate (114), iodobismuthate (115, 117), mercurichloride (39), mercuriiodide (115), reineckate (108, 120, 125), and periodate (123), and that formed with potassium diamminocobaltinitrite (121, 124). Pilocarpine also gives characteristic precipitates with picric (48, 50, 109, 126, 127), styphnic (118, 121, 126, 128), and pierolonic (107, 129) acids, and with trinitro-*m*-cresol (108, 118) and other nitrophenols (118). Many of the precipitation reactions have been adapted for the detection of the alkaloid on the micro scale (111, 119, 121, 122, 130, 131).

Isopilocarpine gives precipitates with auric (28, 50, 109) and platinic (28, 50) chlorides, and with picric acid (28, 50). Isopilocarpine hydrochloride gives a precipitate with mercuric chloride and in this respect differs from pilocarpine hydrochloride (39).

Among the color reactions of pilocarpine, the most characteristic are Helch's test (134, 135, 119, 124) and Ekkert's test (136, 137). Numerous other color reactions are summarized in Table 4.

Helch's test: The pilocarpine solution is treated with a small crystal of potassium dichromate and 1-2 ml. of chloroform, followed by 1 ml. of 3% hydrogen peroxide, and the mixture is shaken for 1-5 minutes. The chloroform layer becomes colored blue.

Ekkert's test: To 1 ml. of a 1% solution of pilocarpine or isopilocarpine hydrochloride are added 1 ml. each of 2% sodium nitroprusside solution and 1*N* sodium hydroxide. After a few minutes the mixture is acidified with dilute hydrochloric

TABLE 4
 COLOR REACTIONS OF PILOCARPINE

Reagent and method	Color observed	References
Ammonium vanadate + $\text{H}_2\text{SO}_4 \cdot \text{H}_2\text{O}$ (Mandelin's reagent) + very dilute P.* solution	Golden yellow \rightarrow green \rightarrow blue	138
Ammonium vanadate + P. HCl + H_2O , cold	Strong yellow	139
Evaporate to dryness, add $\begin{cases} \text{HCl} \\ \text{H}_2\text{SO}_4 \end{cases}$	Red-brown \rightarrow dark green Dark green	
P. + persulfates, heat	Yellow	138, 139
P. + conc. H_2SO_4 (commercial?)	Blue	139
P. + conc. H_2SO_4 (pure)	None	140
P. + 1% KMnO_4 in conc. H_2SO_4	Dark yellow	138
P. + conc. H_2SO_4 + molybdic acid (Fröhde's)	None	140
P. + conc. H_2SO_4 + trace HNO_3 (Erdmann's)	None	140
P. + conc. H_2SO_4 + ammonium selenite	None	141
P. + conc. H_2SO_4 + formaldehyde	Yellow \rightarrow yellow-brown \rightarrow blood- red \rightarrow brown-red. Brown when warmed	138
P. HCl + HCl + ammonium molyb- date, warm	Slight blue	139
P. HCl + HCl + sodium arsenite, heat	Yellow	139
P. HCl + HCl + $\text{K}_3\text{Fe}(\text{CN})_6$ + H_2O , cold	Greenish	139
Add conc. H_2SO_4 , then warm	Dark green \rightarrow blue-black	
P. HCl + $\text{K}_4\text{Fe}(\text{CN})_6$ + H_2O , cold	Strong yellow	139
Add conc. H_2SO_4	Blue	
Evaporate a solution of P. HCl and potassium dichromate and treat residue with HCl	Green	139
Evaporate P. HCl solution with one drop of conc. antimony trichloride solution	Gray to black residue	139
P. HCl + HCl + sodium iodate	Yellow	139
Add conc. H_2SO_4	Dark green	
P. HCl + copper sulfate + H_2O , warm	Green	139
Add H_2SO_4	Blue	
P. + mercuric chloride + 25% HCl , heat	Darkens	139
P. + diazobenzene- <i>p</i> -sulfonic acid (Pauly's)	None	142

* P. = Pilocarpine.

acid; a wine or ruby-red color appears. Half of this solution is treated with a few drops of 0.1 *N* sodium thiosulfate; the color changes to bright green. To the remainder a few drops of 3% hydrogen peroxide or 5 ml. of 0.01 *N* potassium permanganate are added; a carmine-red color is produced. This reaction is also given by the other *jaborandi* alkaloids (137).

A large number of methods have been described for the estimation of pilocarpine, many of which involve the titration of the isolated base with standard acid, using bromophenol blue (98, 99, 143) methyl red (144, 145), methyl orange (98, 146), or dimethyl yellow (98) as indicator. Recovery of the base from its salts for this purpose can be achieved by chromatography on alumina (143). The determination of the acid content of a suitable pilocarpine salt has also been employed, either using phenolphthalein (147), thymolphthalein (97), or Poirrier's blue (103) as indicator, or conductimetrically (148); Volhard's method has been used to estimate the hydrochloride (149). A more specific method of estimation involves the opening of the lactone group by treatment of the alkaloid with hot alkali, followed by titration of the excess alkali (147). An iodimetric method is based on the formation of an insoluble precipitate, $C_{11}H_{16}O_2N_2 \cdot HI \cdot I_5$, when an aqueous solution of a pilocarpine salt is treated with decinormal iodine-potassium iodide solution; after 30 minutes the precipitate is removed and the iodine remaining in solution is titrated (103). Similar methods involve the precipitation of the alkaloid with an excess of Mayer's reagent (112) or silicotungstic acid (150), and estimation of the excess reagent.

Pilocarpine can be estimated gravimetrically by precipitation as the iodobismuthate (110), silicotungstate ($4C_{11}H_{16}O_2N_2 \cdot SiO_2 \cdot 12WO_3 \cdot 2H_2O$) (102, 104), phosphomolybdate (92), picrolonate (129), or nitrate (27, 151, 145). Colorimetric methods of estimation based on Helch's (144) and Ekkert's (137) color reactions have been developed; the reaction of pilocarpine with bromine has also been used as the basis for its estimation colorimetrically (152). Pilocarpine can be estimated polarographically at pH 8.0 in concentrations between 2.0 and 4.0 millimolar (153). Systems for identifying and estimating the alkaloid using steam distillation, volatility, solubility in various solvents, and basic strength have been proposed (154, 155).

For the assay of commercial *jaborandi*, G. R. Lynch and coworkers (145) advise extraction of the drug with chloroform, after the addition of ammonia. The extract is concentrated, diluted with ether, and extracted thoroughly with dilute sulfuric acid. The filtered acid solution is made alkaline with ammonia and the total alkaloids are again taken into chloroform, recovered by evaporation, and estimated alkalimetrically. The pilocarpine content is determined subsequently by quantitative precipita-

tion of the nitrate. In a study of the extraction of pilocarpine from jaborandi preparations for assay purposes, V. Würtzen (146) found that the maximum extraction was obtained by two successive treatments with very dilute hydrochloric acid at 100°; slightly lower (ca. 94%) but consistent results could be obtained by extraction for 30 minutes with 10 equivalents of hot *N*/75 hydrochloric acid. An assay procedure has also been described by Chemnitz (81).

4. PHYSIOLOGICAL PROPERTIES

Owing to its considerable pharmacological importance, the physiological properties of pilocarpine are fully discussed in the standard works on pharmacology. The principal action of the alkaloid is that of a peripheral stimulant of the parasympathetic system, and its action is strongly antagonized by atropine. Conversely, it acts as an antidote to small doses of atropine, but it is ineffective against large doses, and it does not antagonize the action of atropine on the central nervous system.

Pilocarpine increases the secretion of sweat, saliva, tears, and mucus, and of the gastric and pancreatic juices. It causes contraction of the pupil of the eye, and of most smooth muscle, though not that of the blood vessels. In mammals, it causes a transient slowing of the heart, followed by an acceleration and an increase in blood pressure.

Central effects are weak, and late in appearance. Vasomotor paralysis is first apparent, and leads to dyspnea; the emetic center is stimulated causing nausea and vomiting.

Pilocarpine is used principally as a diaphoretic, that is, to induce sweating, especially in nephritis, to relieve the kidneys and to remove toxic metabolites. The secretion of 3 liters of sweat can easily be achieved, and as much as 8 g. of nitrogen can be eliminated. The alkaloid is also employed as a milder substitute for physostigmine in the treatment of ocular diseases. Pilocarpine is reputed to stimulate the growth of hair, and jaborandi extracts are therefore employed to some extent as constituents of hair lotions.

Isopilocarpine is qualitatively similar to pilocarpine in its physiological effects, but is less active.

5. THE INTERCONVERSION OF PILOCARPINE AND ISOPILOCARPINE

Pilocarpine undergoes isomerization to isopilocarpine under a wide variety of conditions. E. Harnack and H. Meyer (23) first observed that pilocarpine undergoes a change when heated alone or with hydrochloric acid. The product was said to be identical with a base which they had already isolated from jaborandi and had named "jaborine," and which was apparently isomeric with pilocarpine. Other investigators (158, 26)

reported similar results, although E. Hardy and G. Calmels (79) considered that the change involved the loss of methyl alcohol. A more complete investigation by A. Petit and M. Polonovski showed that pilocarpine is converted into isopilocarpine (which they named "pilocarpidine") when the base is heated with aqueous sodium hydroxide (51) or better with alcoholic sodium ethoxide (50), or when the hydrochloride is heated at 200° (51). The last reaction was found to proceed without loss of weight, showing it to be an isomerization, and the isomeric relationship of isopilocarpine to pilocarpine was confirmed by the analysis of numerous salts. Pilocarpine is also isomerized by prolonged boiling of aqueous solutions of pilocarpine salts (56), by heating pilocarpine with saturated alcoholic ammonia (56), with alcoholic sodium hydroxide (28), or with water in a sealed tube at 180° for 4 hours (quantitative yield) (28), by distillation of the base or by heating it alone at 200° (56).

The reverse change can also be achieved to a small extent; when isopilocarpine is heated with alcoholic potash for 3 hours, a little pilocarpine can be isolated from the product (35). The nature of the isomerism of the two bases will be discussed in a later section.

A mixture of alcoholic sodium ethoxide (from 1 g. of sodium and 30 ml. of absolute alcohol) and a solution of pilocarpine (3 g.) in absolute alcohol (30 ml.) is heated under reflux for several hours. The alcohol is then removed by distillation and the residue is treated with water. Impurities are removed by extraction with chloroform, and the aqueous phase is acidified, washed with chloroform and basified with aqueous ammonia. The liberated isopilocarpine is extracted with chloroform or benzene, recovered and purified by crystallization of the nitrate from alcohol or water (50).

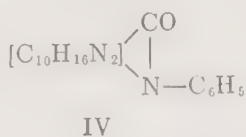
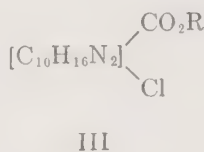
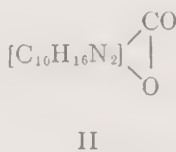
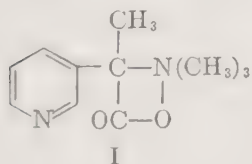
6. DETERMINATION OF STRUCTURE

a. Functional Groups. Pilocarpine and isopilocarpine possess the molecular formula $C_{11}H_{16}O_2N_2$, and analyses of numerous salts indicate that they are only monoacidic bases (23, 26, 28, 50, 156). Pilocarpine contains one methylimino group but no methoxyl group (162). Both bases are unaffected by acetyl chloride (28) and isopilocarpine is not benzoylated by the Schotten-Baumann procedure (39). Alkylation experiments confirm the tertiary nature of the nitrogen atoms, the products obtained with either alkaloid being quaternary salts of the type $C_{11}H_{16}O_2N_2 \cdot RX$ (23, 28, 160).

Isopilocarpine is unaffected by attempted reduction with hot fuming hydriodic acid, sodium in boiling amyl alcohol, zinc and acetic acid or hydrogen bromide in acetic acid (30), and it cannot be reduced electrolytically (33). The absence of an ethylenic linkage is further indicated by the behavior of the two alkaloids towards bromine, the reaction in each case being one of substitution, not addition (30, 39).

The function of the oxygen atoms in the two bases has been established largely by a study of the action of hot aqueous alkali, which indicates the presence of a lactone structure (28, 50). Hardy and Calmels (79) first reported that treatment of pilocarpine with hot aqueous alkali caused the opening of an "internal anhydride," but the further evidence which led them to advance structure I for the alkaloid was later shown to be entirely erroneous (36, 166, 167). Investigations by Petit and Polonovski (50), by Jowett (28), and by A. Pinner and R. Schwarz (39) showed that pilocarpine and isopilocarpine are unaffected by aqueous ammonia or alkali carbonates, but that caustic alkali causes a fall in the specific rotation (see Table 3) due to the formation of salts of pilocarpic and isopilocarpic acids, from the solutions of which the alkaloids cannot be recovered by direct extraction. Amorphous sodium, copper, and barium salts of pilocarpic acid have been isolated (28), and on titration with hot caustic soda both alkaloids show the normal behavior of lactones (33, 50).

Isopilocarpic acid is moderately stable and can be liberated from an alcoholic solution of the potassium salt by saturating with carbon dioxide, filtering, and evaporating under reduced pressure; the residue, which is insoluble in chloroform, analyses as a monohydrate, $C_{11}H_{18}O_3N_2 \cdot H_2O$, and gives a chloroplatinate, $(C_{11}H_{18}O_3N_2)_2 \cdot H_2PtCl_6$. Heating its solution causes reversion to isopilocarpine. Pilocarpic acid is less stable and it cannot be isolated by the above procedure, pilocarpine being regenerated. Even if chloroplatinic acid is added to the neutralized solution before evaporation, only pilocarpine chloroplatinate is obtained (39). However, by treatment of a solution of barium pilocarpate with one equivalent of sulfuric acid, Petit and Polonovski (50) obtained a solution of pilocarpic acid from which nothing could be extracted by chloroform, ether, or benzene, and which showed no change in rotatory power during 24 hours. On evaporation a weakly alkaline sirup was obtained, which was very soluble in water and alcohol, but unlike pilocarpine was insoluble in chloroform, ether, or benzene. Excess of mineral acid converts pilocarpic acid to the corresponding pilocarpine salt, and this slow change can be followed polarimetrically.



Attempts to open the lactone ring in pilocarpine or isopilocarpine (II) by esterification with methyl or ethyl alcohol and excess hydrogen chloride lead to the related chloro esters III (53). Ethyl γ -chloropilocarpate (III, R = Et) can be converted back to pilocarpine by the action of boiling, dilute sulfuric acid. On standing, the chloro esters undergo complex changes probably involving internal quaternary salt formation. With boiling alcoholic sodium ethoxide, the chloro esters are converted into a mixture of the esters of two isomeric α - and β -anhydropilocarpic acids, $C_{11}H_{16}O_2N_2$, the structures of which have not been determined; a cyclopropane structure has been suggested (53). They each contain one acidic and one basic group and are neutral to litmus. Neither acid is isomerized by heating at 250° for 10 minutes, or by heating with alcoholic sodium ethoxide or aqueous acids. Although resistant to reduction by hydrogen and palladium, zinc and hydrochloric acid or sodium amalgam, they are readily oxidized by permanganate in the cold. Bromine reacts with ethyl α -anhydropilocarpate to give a substitution product, $C_{13}H_{19}O_2N_2Br$, from which a crystalline acid, m.p. $138-139^\circ$, is obtained by hydrolysis.

γ -Chloropilocarpic acid (III, R = H) may be an intermediate in the formation of the so-called "pilocarpine anil," $C_{17}H_{21}ON_3$ (IV), by heating pilocarpine hydrochloride with aniline at $205-210^\circ$ (54). This substance is not formed when pilocarpine base is heated with aniline.

b. Oxidation with Permanganate; Isopilopic and Homoisopilopic Acids. Of the various methods which have been employed for the degradation of the jaborandi alkaloids, oxidation with potassium permanganate and fusion with alkali have yielded the most valuable results. Permanganate oxidation was studied independently and almost simultaneously by Jowett (28, 29, 31, 33) and by Pinner and his collaborators (36-39). By the oxidation of isopilocarpine Jowett obtained ammonia, methylamine, and a mixture of two acids, isopilopic* acid, $C_7H_{10}O_4$, and homoisopilopic* acid, $C_8H_{12}O_4$. Acetic and propionic acids were also produced in the oxidation.

Isopilocarpine nitrate (54 g.) is dissolved in water (1 l.) at 80° and a solution of potassium permanganate (188 g.) in water (5 l.) is added gradually with stirring. The manganese dioxide is removed by filtration and is washed well with water, and the filtrate is concentrated to a small volume, made alkaline with sodium hydroxide and distilled until the distillate is no longer alkaline. The residual solution is acidified with hydrochloric acid, steam distilled to remove acetic and propionic acids, evapo-

* These acids were named "pilopic" and "homopilopic" acids by Jowett. Since they are stereochemically related to isopilocarpine, W. Langenbeck (168) proposed that their names should be changed to isopilopic and homoisopilopic, the original names being assigned to the corresponding acids related stereochemically to pilocarpine. Throughout this chapter the older nomenclature has been altered to conform with the modern usage.

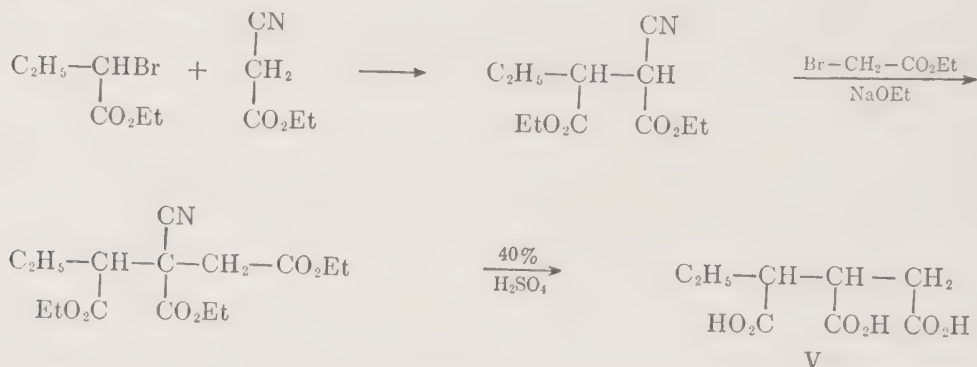
rated, and mixed with sand. After thorough drying, the mixture is extracted with absolute alcohol in a Soxhlet apparatus. The extract is saturated with hydrogen chloride and, after being allowed to stand, is boiled under reflux for 2 hours. The resulting mixture of esters is separated by distillation into three fractions: (a) b.p. 290–300°, (b) b.p. 300–310°, and (c) a small fraction of b.p. 310–312°. Fraction (a), which analyzes as $C_9H_{11}O_4$, yields on hydrolysis isopilopie acid, m.p. 104° (corr.) (70% yield). Fraction (c), analyzing as $C_{10}H_{16}O_4$, consists chiefly of ethyl homoisopilopate since it gives homoisopilopie diamide, m.p. 208° (corr.) on treatment with ammonia. Fraction (b) is a mixture of the two esters.

By the oxidation of pilocarpine with permanganate, A. Pinner and E. Kohlhammer (36–38) also obtained ammonia and methylamine, together with a nitrogen free acid, a neutral substance, $C_2H_6ON_2$ (probably *N*-methylurea (39)), and other unidentified products. Difficulty was experienced in assigning a molecular formula to the acidic product, which was first named “piluvic acid” and subsequently “homopilomalic acid.” Finally, Pinner and Schwarz (40) accepted Jowett’s suggestion (31, 33) that the product was a mixture of isopilopie and homoisopilopie acids, and Jowett (33) confirmed that homoisopilopie acid was produced from pilocarpine as well as from isopilocarpine by oxidation. The foregoing investigations proved the earlier work of Hardy and Calmels (79) to be entirely erroneous.

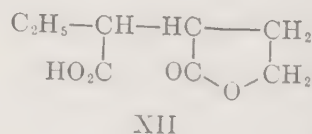
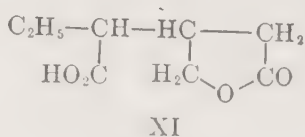
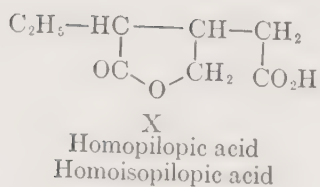
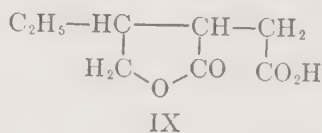
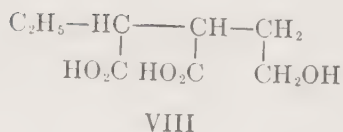
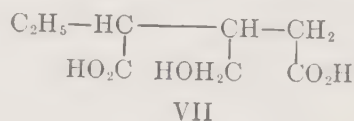
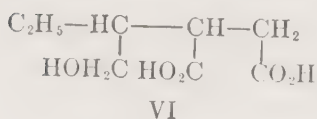
Isopilopie acid, $C_7H_{10}O_4$, is a crystalline substance, freely soluble in water, alcohol or benzene (129, 131). It is dextrorotatory but is partially racemized; pure *d*-isopilopie acid can be obtained by crystallization of the strychnine salt (57). On titration in the cold, it behaves as a monobasic acid, but it reacts with two molecular proportions of hot aqueous alkali, indicating that it retains the lactonic structure of the alkaloids. Confirmation of its lactonic nature is afforded by its conversion by boiling aqueous barium hydroxide to the barium salt, $C_7H_{10}O_5Ba \cdot H_2O$, of the related hydroxy acid; the analogous silver salt, $C_7H_{10}O_5Ag_2$, has also been prepared (29). Isopilopie acid is unaffected by boiling concentrated hydriodic acid, and an attempt to elucidate its fundamental carbon skeleton by treating ethyl isopilopate with phosphorus pentabromide, debrominating the product with diethylaniline, and oxidizing successively with potassium permanganate and chromic acid, led only to a small yield of a butyric acid (29). When isopilopie acid is fused with potassium hydroxide at a moderate temperature, it is isomerized to an acid of undetermined structure; at a higher temperature, *n*-butyric acid is obtained (31).

The degradation of the liquid homoisopilopie acid, $C_8H_{12}O_4$, leads to more significant results. Like its lower homologue, this acid is shown to possess a lactone grouping by its behavior towards alkali, and by the isolation of the barium salt, $C_8H_{12}O_5Ba$, and the diamide of the related

hydroxy acid. Homoisopilopic acid is stable towards chromic acid (38), but on fusion with potash at a moderate temperature, it yields (31) a crystalline, optically inactive, tribasic acid, $C_8H_{12}O_6$, shown to be identical with *dl*- α -ethyltricarballic acid (V), synthesized (32) by the following route:

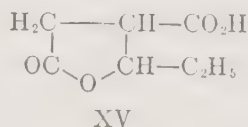
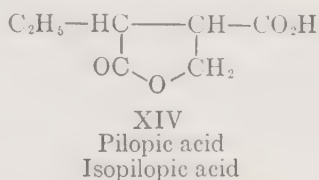
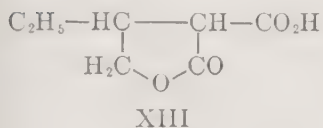


The conversion of homoisopilopic acid into ethyltricarballic acid occurs without loss of carbon, and thus involves the oxidation to carboxyl of a primary alcoholic group in the derived hydroxy-dicarboxylic acid, which must therefore possess one of the structures (VI), (VII), or (VIII). In view of the stability of homoisopilopic acid towards cold alkali, Jowett suggested it to be a γ - rather than a δ -lactone, and four structures (IX)–(XII) for the acid thus come into consideration. By a careful consideration of the course of the permanganate oxidation of isopilocarpine, Jowett



concluded that isopilopic acid is a product of the further oxidation of homoisopilopic acid, and that the latter substance must therefore contain the group $-\text{CH}_2-\text{CO}_2\text{H}$. Structures XI and XII are accordingly

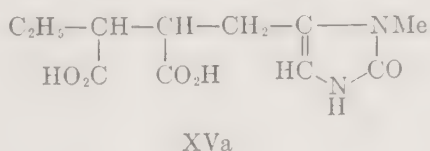
excluded. A decision between the remaining structures (IX) and (X) may be reached by a consideration of the properties of isopilopie acid, the corresponding structures for which are XIII and XIV. A substance of structure XIII would readily lose carbon dioxide on heating, since it is a derivative of malonic acid. Isopilopie acid, however, is stable at 200°, and in its general properties it resembles the known ethylparaconic acid (XV). It must therefore be assigned the structure XIV, and homo-isopilopie acid is accordingly X.



c. Effect of Other Oxidizing Agents. Pilocarpine is oxidized by 30% hydrogen peroxide with the formation of ammonia, methylamine, carbon dioxide and crude homoisopilopie acid (37). It is unaffected by cold fuming nitric acid; on heating with this reagent, it is merely isomerized to isopilocarpine, which is only oxidized to a slight extent (28).

Chromic acid attacks the alkaloids only very slowly. Jowett (30) recovered isopilocarpine unchanged after it had been treated with chromic acid at room temperature for several days, and Pinner and Schwarz (39) found that heating on the water bath for 7 days was necessary for the complete oxidation of this base with excess chromic acid; the products were not examined. A solution of pilocarpine in dilute sulfuric acid, on heating with chromic acid, consumed four atomic proportions of oxygen in 6 hours, giving 50–60% of an acid, pilocarpoic acid (37, 39), and a trace of a second product, $\text{C}_8\text{H}_{10}\text{O}_2\text{N}_2$ or $\text{C}_8\text{H}_{12}\text{O}_2\text{N}_2$, which was not further examined; ammonia, methylamine and carbon dioxide were not formed in the oxidation.

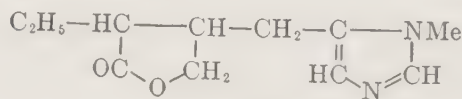
Pilocarpoic acid, $\text{C}_{11}\text{H}_{16}\text{O}_5\text{N}_2$, isolated through its barium salt, is converted by heat into isopilocarpoic acid; it can also be converted into an anhydride, $\text{C}_{11}\text{H}_{14}\text{O}_4\text{N}_2$ (41). The structures of these substances have not been fully elucidated, but Pinner (41) suggested the structure (XVa) for pilocarpoic acid. Barium pilocarpoate, on further oxidation with permanganate, yields an optically active, nitrogen-free acid, originally (38) named "isohydrochelidonic acid," but eventually (39, 41) named



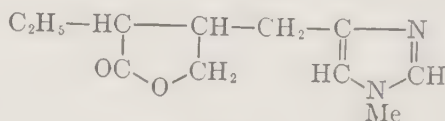
pilomalic acid and assigned the formula $C_8H_{12}O_6$; its constitution has not been rigidly established, but it is probably an optically active α -ethyl-tricarballic acid (V).

d. Alkaline Degradation: the Imidazole Nucleus. The results of earlier work (23, 157) on the fusion of pilocarpine with alkalis were for the most part confirmed by the more thorough investigations of Jowett (28, 29) and of Pinner and Schwarz (40). Neither pilocarpine nor isopilocarpine breaks down on prolonged heating with 30% aqueous potassium hydroxide, or on treatment with barium hydroxide at 160° (40), but when isopilocarpine nitrate is fused with an excess of potassium hydroxide, ammonia, methylamine, and butyric acid are formed (28, 29). The quaternary salts derived by treating the alkaloids with alkyl halides are considerably less stable towards alkali, and are decomposed to methylamine, the alkylamine, formic acid and homoisopilopic acid (X) on heating with 30% aqueous potash (28, 29, 40).

In their ready oxidation by permanganate or hydrogen peroxide, their stability to chromic acid and their behavior on bromination (see Section 7a), and in their degradation and that of their quaternary salts by alkali, the alkaloids closely resemble known imidazole derivatives, and Pinner and Schwarz (40) consequently proposed structure XVI for pilocarpine.



XVI
Pilocarpine
Isopilocarpine

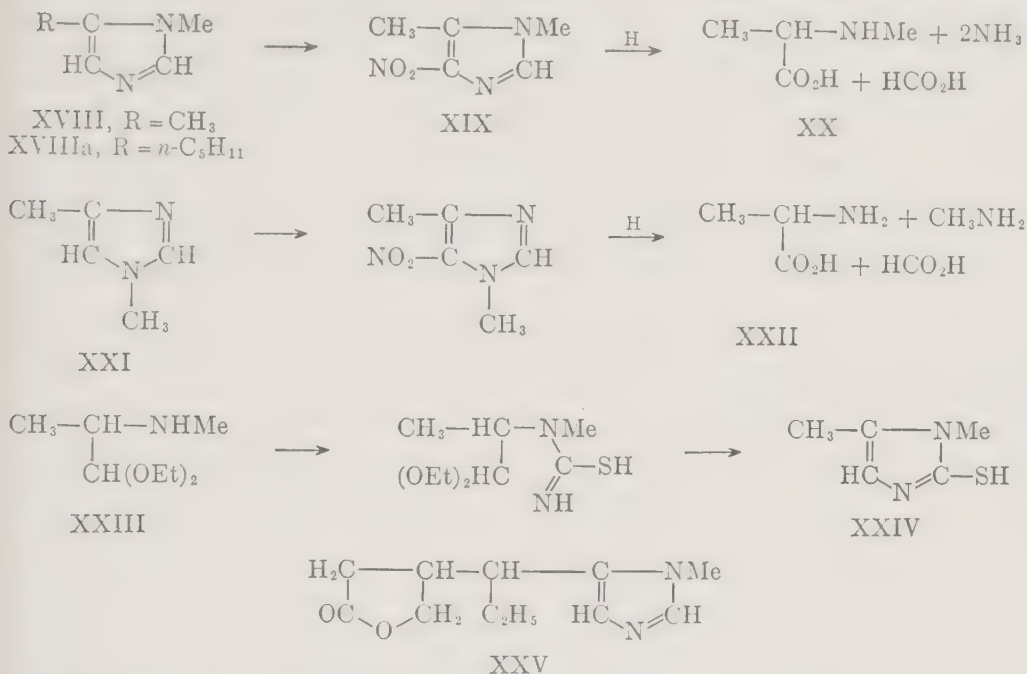


XVII

The presence of an imidazole nucleus in the alkaloids was confirmed by Jowett (33) by distilling isopilocarpine with soda lime, when, in addition to ammonia and methylamine, three bases were formed. The first was identical with the known 1-methylimidazole. The second, $C_5H_8N_2$, yields ammonia, methylamine and acetic acid on oxidation with permanganate, and is therefore a dimethylimidazole, and it proved to be very similar to one of the dimethylimidazoles obtained by *N*-methylation of 4(5)-methylimidazole (34, 44). The third base, $C_9H_{16}N_2$, yields *n*-hexanoic acid on oxidation with permanganate and thus appears to be a *n*-amyl-1-methylimidazole.

The uncertainty regarding the orientation of the synthetic dimethylimidazoles rendered it impossible at this stage to decide between the structures XVI and XVII for isopilocarpine. This difficulty was resolved by F. L. Pyman (47), who succeeded in determining the orientation of the dimethylimidazoles by degradation. The base from iso-

pilocarpine yields a nitro derivative (XIX), which on reduction with an acid solution of stannous chloride undergoes ring fission, giving *dl*-*N*-methylalanine (XX). Hence this base is 1:5-dimethylimidazole (XVIII), and isopilocarpine must be XVI. In confirmation, the isomeric (synthetic (44)) dimethylimidazole (XXI) was degraded in a similar fashion to *dl*-alanine (XXII), and finally R. Burtles, F. L. Pyman, and J. Roylance (48) synthesized 1:5-dimethylimidazole by an unequivocal method.

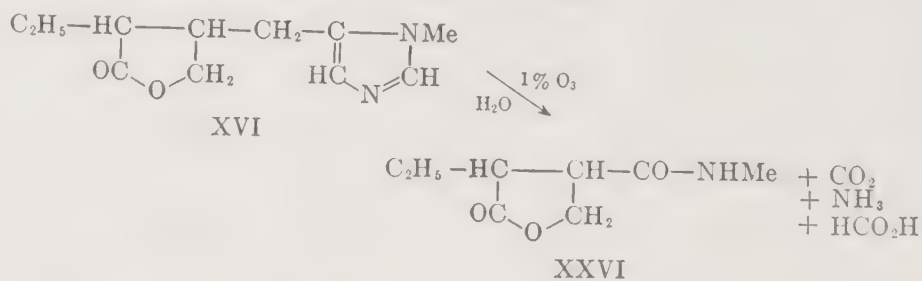


Interaction of α -methylaminopropionacetal (XXIII) with thiocyanic acid gave 2-thiol-1:5-dimethylimidazole (XXIV), which on treatment with hot 10% nitric acid was desulfurized to the desired base (XVIII). Subsequently, S. Akabori and S. Numano (171) synthesized 1-methyl-5-*n*-amylimidazole (XVIIIa) by a similar route and showed the product to be identical with the base, $\text{C}_9\text{H}_{16}\text{N}_2$, arising from the distillation of isopilocarpine with soda lime. The identification of this product serves to exclude a third structure (XXV) for isopilocarpine, which is otherwise consistent with much of the evidence so far presented.

e. Relation of Pilocarpine to Isopilocarpine. The foregoing investigations serve to establish rigidly the structure of isopilocarpine only, and do not disclose the nature of its relationship to pilocarpine. Jowett (28, 29) suggested that the relationship was purely stereochemical, but Pinner and Schwarz (39, 40) maintained that the two bases were structural isomerides (XVI) and (XVII) differing in the position of the *N*-methyl group, this view being based on their differences in behavior towards

chromic acid (Section 6c) and towards hot aqueous bromine (Section 7a). Pinner (41) also drew support for his contention from the fact that the two alkaloids give rise to two different series of derivatives only so long as the imidazole ring is intact; when the heterocyclic nucleus is destroyed, the same products are obtained from either alkaloid. Pinner's views were criticized by Jowett (33, 35) largely on the grounds that they were incompatible with the ready and reversible conversion (see Section 5) of pilocarpine into isopilocarpine, which could not be reconciled with the stability of the known 1:2-, 1:4-, and 1:5-dimethylimidazoles. The formation of identical products in the permanganate oxidation can be ascribed to the use of conditions favorable to isomerization during the isolation of these products. M. and M. Polonovski (56) added some support to Jowett's theory by observing that derivatives of pilocarpine in which the lactone ring has been opened are not isomerized by alcoholic sodium ethoxide; the isomerism thus appears to be associated with the lactone group.

Elegant work by W. Langenbeck (168) provided clear evidence that the two alkaloids are stereoisomers. First, he showed that the quaternary salts formed by methylating the two alkaloids are not identical, whereas the structures XVI and XVII would, like 1:4- and 1:5-dimethylimidazole (44), give identical metho salts. He then subjected each alkaloid to ozonolysis; isopilocarpine yielded the methylamide XXVI of the known homoisopilopie acid, but pilocarpine gave rise to the methylamide of the hitherto unknown homopilopie acid, in 97% yield. Thus the isomerism shown by the two alkaloids persists when the imidazole ring is destroyed under mild conditions, and it must therefore be due to a stereochemical difference in the lactonic portion of the molecule. Furthermore, the isolation of methylamides from both alkaloids confirms the 1:5 orientation of substituents in the imidazole nucleus.



7. SUBSTITUTION PRODUCTS AND OTHER DERIVATIVES

a. Halogenation. The action of halogens on pilocarpine was first investigated by P. Chastaing (159, 161); with chlorine or bromine in chloroform he obtained the weakly basic dichloro- or dibromopilocarpine, isolated respectively as the perchloride or perbromide. The same bro-

mination product was subsequently obtained by Jowett (30) and by Pinner and Kohlhammer (36), by treatment of the alkaloid with bromine in 80% acetic acid. Isopilocarpine is similarly converted by bromine in water, chloroform or 80% acetic acid into the perbromide of dibromoisopilocarpine, together with lesser amounts of a monobromo derivative, and an acid, isopilocarpinic acid, $C_{11}H_{16}O_4N_2$, which has not been further investigated (30, 41).

Pilocarpine and isopilocarpine are regenerated quantitatively when their dibromo derivatives are reduced with sodium and amyl alcohol or with zinc and acetic acid. Hydrolytic removal of the bromine atoms with hot 10% aqueous barium hydroxide is accompanied in each case by extensive degradation of the molecule, with liberation of ammonia and methylamine (36, 39, 40); under milder conditions both dibromopilocarpine and dibromoisopilocarpine yield barium dibromoisopilocarbate by the opening of the lactone ring, accompanied in the former case by isomerization. On treatment of the barium salt with acetic acid, dibromoisopilocarpic acid is obtained; this acid lactonizes less readily than isopilocarpic acid, since it is reconverted into dibromoisopilocarpine only on heating. Oxidation of the dibromoisopilocarpine with permanganate produces isopilopic acid, together with ammonia, methylamine, and a monobasic, lactonic acid, isopilopinic acid ("pilopinic acid"*), $C_8H_{11}O_4N$, of unknown structure, which is further oxidized to ammonia and isopilopic acid. Bromination thus occurs exclusively in the imidazole ring, the dibromo alkaloids having the structure XXVII. H. Pauly and E. Arauner (172) have shown that, when imidazoles are brominated, the 4(5)-position is the first to be attacked, and the direct bromination of the alkaloids doubtless follows the same course. On the other hand, when treated with cyanogen bromide, pilocarpine and isopilocarpine undergo bromination at the 2-position of the imidazole nucleus (169).

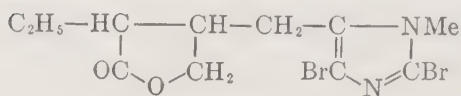
Treatment of isopilocarpine with aqueous bromine at 90–140° causes both bromination and oxidation giving a monobasic acid, dibromoisopilocarpinic acid, $C_{11}H_{14}O_4N_2Br_2$, of undetermined constitution, together with ammonia, methylamine and other unidentified products. On treatment with zinc and acetic acid, dibromoisopilocarpinic acid yields the nonbasic isopilocarpinolactone, $C_{11}H_{14}O_4N_2 \cdot H_2O$, apparently by the replacement of one bromine atom by hydrogen and the other by hydroxyl; the product yields a silver salt, $C_{11}H_{15}O_5N_2Ag$, and is oxidized by permanganate to isopilopic acid (30, 33).

According to Pinner and Kohlhammer (36) treatment of pilocarpine with aqueous bromine at 100° gives rise to a dibasic acid, bromocarpinic acid, $C_{10}H_{15}O_4N_2Br$, and other products, but Jowett (30) was unable to

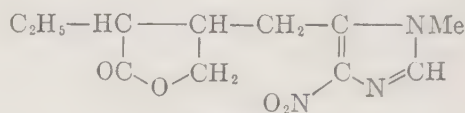
* Compare footnote on p. 216.

confirm this. The behavior of bromocarpinic acid towards saturated aqueous barium hydroxide (36, 37, 41), potassium permanganate (38) and barium carbonate (40) has been investigated without significant result. Structures have been proposed by Pinner (41) for the various products mentioned above (based on the incorrect structure (XVII) for isopilocarpine), but further investigation appears to be required.

An iodopilocarpine has been obtained by the direct iodination of the alkaloid in chloroform solution (161).



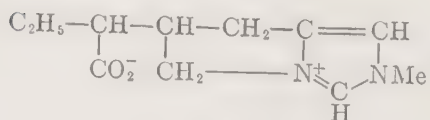
XXVII



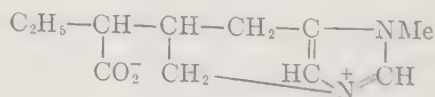
XXVIII

b. Nitration. By treating the alkaloidal nitrates with concentrated sulfuric acid at 0°, M. and M. Polonovski (52) obtained mononitro derivatives of pilocarpine and isopilocarpine. By analogy with the course of the nitration of 1:5-dimethylimidazole (47) these substances may be assigned the structure (XXVIII). Nitropilocarpine is isomerized to nitroisopilocarpine by sodium ethoxide; both substances are weak bases and in both the lactone ring can be opened by aqueous alkali. Reduction of nitropilocarpine by acidified stannous chloride or other reagents causes fission of the imidazole ring with liberation of ammonia. The imidazole nucleus is also degraded when the nitro alkaloids are heated with concentrated aqueous barium hydroxide, isopilocarpic and homoisopilocarpic acids being formed, together with formic acid, ammonia, and methylamine.

c. Metapilocarpine. This substance was first obtained by Pinner (42) by heating pilocarpine hydrochloride at 225–235° for 1 to 2 hours, and was subsequently further examined by M. and M. Polonovski (55). It is an optically inactive, amorphous substance, $\text{C}_{11}\text{H}_{16}\text{O}_2\text{N}_2 \cdot \text{H}_2\text{O}$, insoluble in chloroform, but readily soluble in water to give a neutral solution. It forms no salts with alkalies, but is readily degraded by hot alkali to methylamine and a nitrogenous acid. It forms salts with acids, of which only the chloroplatinate is crystalline; these salts have an acid reaction. M. and M. Polonovski (55) proposed a betaine structure (XXIX) for metapilocarpine, but this is based on the incorrect structure (XVII) for pilocarpine; a similar structure (XXX) derived from (XVI) is sterically impossible, and the nature of metapilocarpine thus requires further investigation.



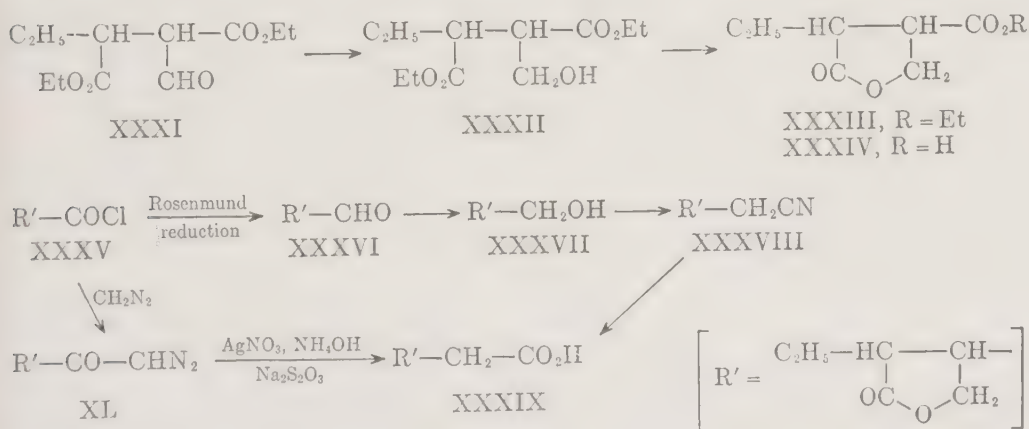
XXIX



XXX

8. SYNTHESIS OF PILOCARPINE AND ISOPILOCARPINE

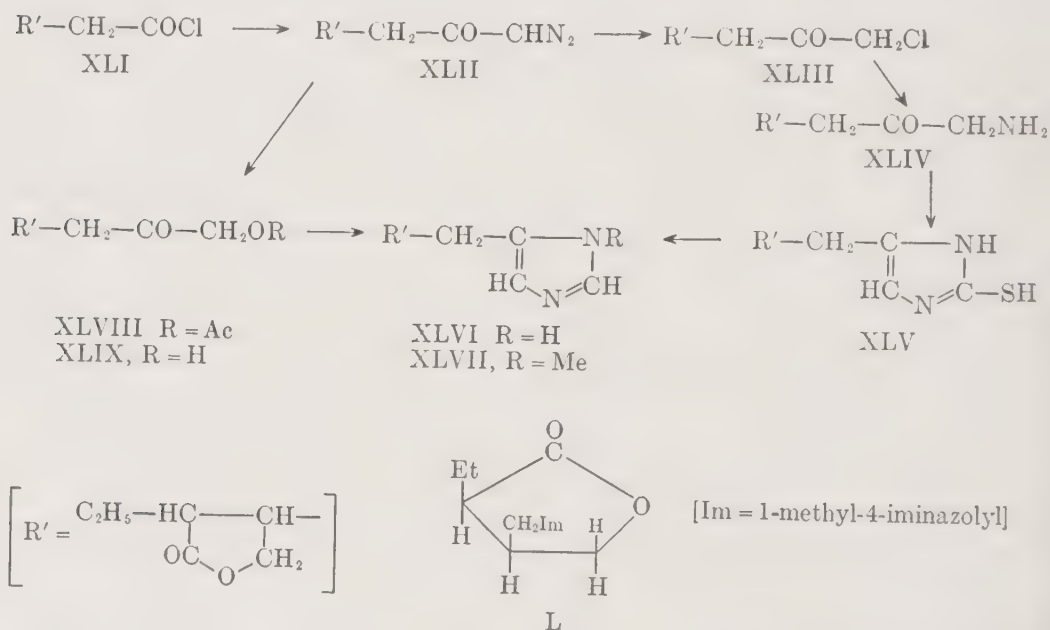
The structures assigned to the alkaloids and their breakdown products on the basis of the degradative evidence have been confirmed by the synthetic investigations of N. A. and W. A. Preobrashenski and their collaborators. The first step, the synthesis of pilopie and isopilopie acids, was achieved in 1930 by A. E. Tschitschibabin and N. A. Preobrashenski (57). In the original synthesis, ethyl α -formyl- α' -ethylsuccinate (XXXI) was reduced with aluminum amalgam and moist ether to the hydroxy ester (XXXII), which lactonized on heating, forming a mixture of the two racemic forms of the ester (XXXIII), one being a liquid and the other a solid. Hydrolysis of the liquid ester gave an acid which was not isomerized by heat, and which was accordingly recognized as *dl*-isopilopie acid (XXXIV); other routes leading to the synthesis of this acid have been described by K. N. Welch (173) and by A. M. Poljakova and N. A. Preobrashenski (69). On resolution through the strychnine salt, the *d*- and *l*-forms were obtained, the former being identical with *d*-isopilopie acid obtained by the oxidation of isopilocarpine and purified through the strychnine salt. The solid ester (XXXIII) similarly gave *dl*-pilopie acid, which is readily isomerized to *dl*-isopilopie acid when heated (61). It was resolved through the brucine and cinchonine salts (62).



dl-Isopilopie acid was converted into *dl*-homoisopilopie acid by the series of reactions depicted in the formulas XXXV to XXXIX (60). Because of its ready isomerization, *d*-pilopie acid could not be subjected to the same procedure (61), but *d*-homopilopie acid was obtained from it by the Arndt-Eistert method of homologation through the diazo ketone (XL) (63). The product was identical with that obtained from pilo-

carpine, and it was quantitatively isomerized to *d*-homoisopilocarpic acid by distillation under reduced pressure (59).

The final stages in the synthesis of pilocarpine were achieved by N. A. and W. A. Preobrashenski, A. F. Wompe, and M. N. Schtschukina (59). *d*-Homopilocypyl chloride (XLI) was converted through the diazo ketone (XLII) into *d*-homopilocypyl chloromethyl ketone (XLIII), and thence by Gabriel's phthalimide method into the amino ketone XLIV. The imidazole nucleus was constructed by the interaction of the hydrochloride of XLIV with potassium thiocyanate, and the resulting 2-thiol-4(5)-*d*-homopilocypylimidazole (XLV), when desulfurized with hot aqueous ferric chloride, yielded *d*-pilocarpidine (XLVI). Methylation then afforded *d*-pilocarpine (XLVII), identical in all respects with the natural alkaloid (see Table 5). Isopilocarpine was also synthesized by the same method (58).



This synthesis was subsequently shortened (67); interaction of the diazo ketone, XLII, with acetic acid gave an acetate (XLVIII), hydrolyzed to the keto alcohol (XLIX), treatment of which with copper acetate, ammonia, and formaldehyde gave *d*-pilocarpidine (XLVI). This method has also been applied to the synthesis of 2-alkyl derivatives of pilocarpine.

N. A. and W. A. Preobrashenski and A. M. Poljakova (66) have published a general survey of their synthetic investigations and have also proposed a method for the synthesis of pilocarpine on the technical scale. From a consideration of the optical rotations of the various products, they suggest that pilocarpine possesses the *cis*-configuration (L), isopilocarpine having the corresponding *trans*-configuration.

TABLE 5

PHYSICAL CONSTANTS OF SYNTHETIC ALKALOIDS AND DERIVATIVES, AND COMPARISON
WITH SPECIMENS FROM NATURAL SOURCES

Substance	Synthetic specimen			Specimen from natural source*		
	M.p., °C.	$[\alpha]_D$	Ref.	M.p., °C.	$[\alpha]_D$	Ref.
<i>dl</i> -Pilopie acid	90-91		57			
<i>dl</i> -Isopilopie acid	87.5-88		57			
<i>d</i> -Pilopie acid	121.2-122.2	+54.6°	62			
<i>l</i> -Pilopie acid	120.0-121.8	-54.0°	62			
<i>d</i> -Isopilopie acid	105-105.5	+58.92°	57	105-105.5	+58.93°	57
<i>l</i> -Isopilopie acid	105-105.5	-58.06°	57			
<i>dl</i> -Homopilopie acid	100-101		61			
	106-107		65			
<i>dl</i> -Homoisopilopie acid	74.2		60			
<i>d</i> -Homopilopyl chloro- methyl ketone	88.5-89.2		63	88.5-89.2		63
<i>d</i> -Homoisopilopie acid		+50.98°	58			
<i>dl</i> -Pilocarpidine nitrate	128-129		65			
<i>d</i> -Pilocarpidine nitrate	132.5-133	+71.78°	59	134-136	+73.2°	109, 28
<i>dl</i> -Isopilocarpidine nitrate	114-114.5		64			
<i>d</i> -Isopilocarpidine nitrate	112-113.5	+27.63°	58	109-111		109
<i>dl</i> -Pilocarpine nitrate	139-140		65			
<i>d</i> -Pilocarpine nitrate	175.5-176.5	+82.64°	59	175-175.5	+81.09°	59
<i>dl</i> -Isopilocarpine nitrate	134-135		64			
<i>d</i> -Isopilocarpine nitrate	158-158.5	+55.62°	58	158-159.8	+52.74°	58

* The data are for the pure *d*-forms, prepared through the strychnine salts, and differ somewhat from the normal values.

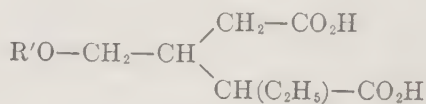
A. N. Dey (174) has described an independent synthesis of the alkaloids. Michael condensation of ethyl γ -ethoxy- or γ -phenoxy-crotonate (LI, R = OEt, R' = Et or Ph) with ethyl malonate or cyanacetate, followed by ethylation and hydrolysis, furnished a mixture of the two racemic forms of the glutaric acid, LII, which were separated by virtue of their different ease of anhydride formation. On treatment with hydrobromic acid, they gave rise to *dl*-homopilopie acid and *dl*-homoisopilopie acid (LIII, R = OH), respectively. Corresponding methyl ketones (LIII, R = Me) were obtained by a similar synthesis from 1-ethoxypent-2-en-4-one (LI, R = Me, R' = Et), and by the action of methylzinc iodide on the homopilopoyl chloride or homoisopilopoyl chloride. They gave benzylidene derivatives which on ozonolysis afforded the glyoxal derivatives, LIV, converted by reaction with

ammonia and formaldehyde into *dl*-pilocarpidine and *dl*-isopilocarpidine (XLVI), which were then methylated. Resolution of the resulting *dl*-pilocarpine was readily achieved through the tartrates, and the optically active forms could be isomerized by alkali to give *d*- and *l*-isopilocarpine.

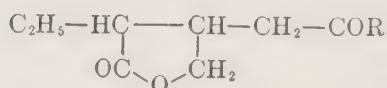
Various analogues of pilocarpine have also been synthesized, for example, the substances LV (175), LVI (70), LVII (71), LVIII, and LIX (45).



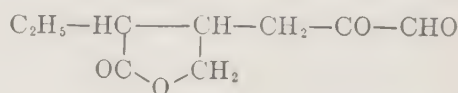
LI



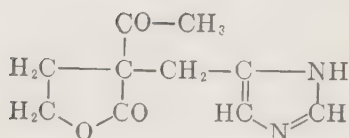
LII



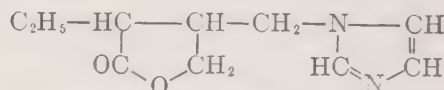
LIII



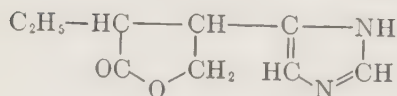
LIV



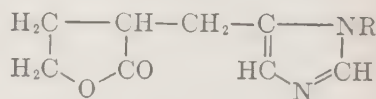
LV



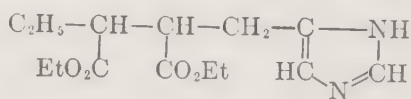
LVI



LVII



LVIII, R = H or Me

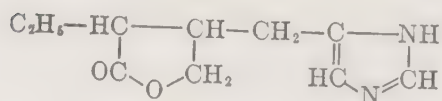


LIX

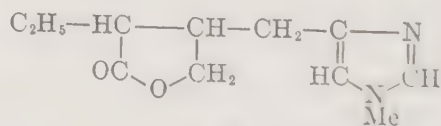
IV. Pilocarpidine

1. OCCURRENCE AND ISOLATION

The alkaloid pilocarpidine was first isolated from jaborandi by E. Merck (165, 166) from the mother liquors remaining after the isolation of pilocarpine, and this material was investigated by E. Harnack (24, 26).



I



II

Subsequently, H. A. D. Jowett (28) confirmed the findings of Merck and Harnack, but showed that pilocarpidine was not present in the leaves of *P. microphyllus*, nor in the samples of *P. jaborandi* available at the time of his investigation. Commercial pilocarpine nitrate was also shown to contain no pilocarpidine. Pilocarpidine is freed from accompanying bases by fractional crystallization of the nitrate.

The use of the name "pilocarpidine" by A. Petit and M. Polonovski (50) for the alkaloid now known as isopilocarpine has caused some confusion in the literature.

2. PHYSICAL, CHEMICAL AND PHYSIOLOGICAL PROPERTIES

Pilocarpidine is a colorless, strongly alkaline, deliquescent sirup (26, 165) which forms crystalline salts (see Table 7). It is readily soluble in water, ethyl and amyl alcohols, chloroform and ethyl acetate, sparingly soluble in ether and benzene and insoluble in light petroleum. It is optically active, the specific rotations of the base and its salts being shown in Tables 6 and 9. Pilocarpidine turns yellow on exposure to light and darkens on heating in air.

Merck (166) observed that pilocarpidine underwent a change when heated at 200–205°, and Harnack (26) found that, under various conditions, it could be transformed into a new base which he named "jaboridine." Subsequently, E. Späth and R. Kunz (109) showed that, like pilocarpine, pilocarpidine is converted by sodium ethoxide into the stereoisomer isopilocarpidine, and Harnack's "jaboridine" was presumably somewhat impure isopilocarpidine.

Pilocarpidine is precipitated from acid solution by phosphotungstic acid (26), silicotungstic acid (104), auric chloride (28, 109, 164, 165), platinic chloride (28, 165), trinitro-*m*-cresol and Reinecke's salt (108). The silicotungstate ($4\text{C}_{10}\text{H}_{14}\text{O}_2\text{N}_2\cdot\text{SiO}_2\cdot 12\text{WO}_3\cdot 2\text{H}_2\text{O}$) is used for the gravimetric estimation of the alkaloid. The aurichloride is more soluble than that of pilocarpine, which may account for the early report (26) that the alkaloid is not precipitated by auric chloride. The Ekkert color reaction (p. 210) is given as strongly by pilocarpidine as by pilocarpine (137). Microchemical tests for pilocarpidine have been described by L. Rosenthaler (119) and A. Bolland (133). The detection of pilocarpidine in the presence of a greater amount of pilocarpine is difficult (108).

The physiological action of pilocarpidine is qualitatively similar to, but much weaker than, that of pilocarpine (25, 26). Pilocarpidine is iodinated by iodine in potassium iodide solution, in the presence of potassium carbonate, to give 2-iodopilocarpidine (172), which, like

2-iodo-4(5)-methylimidazole, reduces the body weight of rats when administered orally (176).

3. STRUCTURAL INVESTIGATION

Pilocarpidine has the molecular formula $C_{10}H_{14}O_2N_2$. It is thus the lower homologue of pilocarpine, and since it contains no methylimino group (163, 164), and gives a deep red color with Pauly's histidine reagent (diazobenzene-*p*-sulfonic acid) (46), indicative of a free imino group, it was suggested that pilocarpine is *N*-methylpilocarpidine (26, 46). Neither Harnack (26) nor Merck (165) were able to confirm this by the methylation of pilocarpidine, but subsequently Burtles, Pyman, and Roylance (48) and also Späth and Kunz (109) obtained pilocarpine by the interaction of pilocarpidine (I) and methyl iodide under mild conditions. The former group also isolated the isomer, neopilocarpine (II), as a second product of the methylation, the reaction being analogous to the production of both 1:4- and 1:5-dimethylimidazoles by the methylation of 4(5)-methylimidazole. Neopilocarpine shows none of the typical physiological action of pilocarpine, and possesses merely a weak stimulating action on isolated intestinal muscle (48). It is converted by alkali into the stereoisomeric isoneopilocarpine. (See p. 228 for formulas I, II.)

Späth and Kunz also methylated isopilocarpidine and obtained the methiodide of isopilocarpine; the stereochemical relationships of the various bases are thus completely established. The structure (I) assigned to pilocarpidine is further confirmed by its synthesis, which has been described above (Section II, 8).

V. Pilosine

1. OCCURRENCE AND ISOLATION

The minor alkaloid pilosine was isolated from *Pilocarpus microphyllus* by F. L. Pyman (46) and independently by E. Léger and F. Roques (116, 117) who named it "carpine." The crude alkaloid was obtained by fractional precipitation of the bases remaining in the mother liquor after the removal of pilocarpine and isopilocarpine, and it was purified by crystallization from 90% alcohol. The yield corresponded to a content of only 0.007% of the leaves, and it was established that no other alkaloid was present in the leaves in quantity greater than 0.003% (46).

2. PHYSICAL, CHEMICAL AND PHYSIOLOGICAL PROPERTIES

Pilosine is a crystalline, optically active base that is readily soluble in chloroform or benzene and more sparingly so in ether; it crystallizes

from alcohol or water. The salts crystallize with difficulty, but the hydrochloride, sulfate, hydrogen tartrate, and aurichloride have been obtained in crystalline form (46, 116). (See Table 7.) Pilosine is alkaline to litmus but not to phenolphthalein, and the base is soluble in water saturated with carbon dioxide (116).

The specific rotation of an aqueous solution of pilosine falls when the solution is allowed to stand, and it is profoundly altered by the addition of acid or alkali; data regarding the optical activity of the alkaloid and its degradation products are included in Table 6. (See also Table 9.)

TABLE 6
EFFECT OF ACID AND ALKALI ON THE OPTICAL ROTATORY POWER OF THE
MINOR JABORANDI ALKALOIDS AND THEIR DERIVATIVES

Substance	[α] _D of the solution in		
	Water	Acid	Alkali
Pilocarpidine	+81.3°	+97.0°	+ 35.2°
Pilosine	+39.9°	+24.6°	- 67.6°
Anhydropilosine	+66.2°	-20.8°	-132.7°
Pilosinine	+14.2°	+ 5.8°	- 5.8°

In physiological action pilosine and anhydropilosine (see below) possess a very weak pilocarpine-like effect; the degradation product pilosinine has a somewhat stronger action, but its activity still falls far short of that of pilocarpine (46).

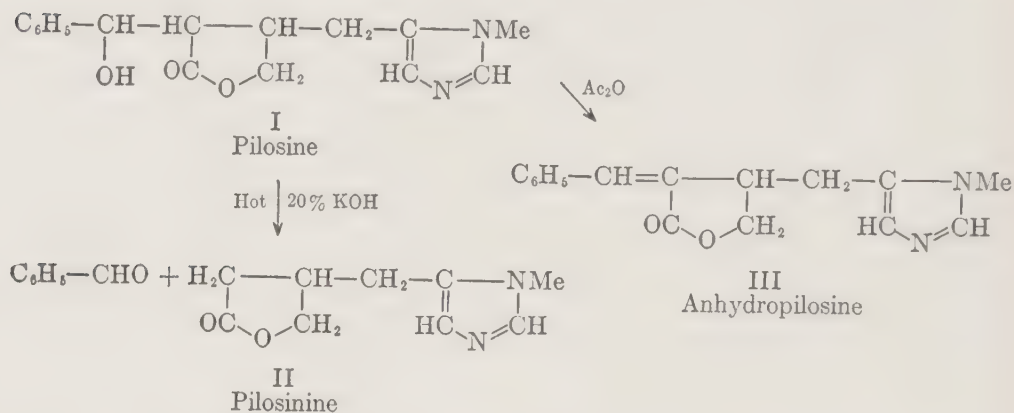
3. STRUCTURAL INVESTIGATION

Pilosine has the molecular formula $C_{16}H_{18}O_3N_2$ and is a monoacidic base which contains one *N*-methyl group, no imino group and no methoxyl group. The presence of a lactonic structure is shown by titration with hot alkali. The alkaloid also contains an alcoholic hydroxyl group, the presence of which is indicated by the preparation of an amorphous benzoyl derivative, and by the dehydration of the alkaloid with hot acetic anhydride to anhydropilosine, $C_{16}H_{16}O_2N_2$. This optically active, monoacidic base still contains the lactone structure, but unlike pilosine it is immediately oxidized by cold aqueous potassium permanganate (46, 116).

Pilosine is unaffected by dilute sulfuric acid at 140° (116), and boiling 5% aqueous sodium hydroxide merely opens the lactone ring (46), but when treated with boiling 20% aqueous potassium hydroxide it is degraded to benzaldehyde and a new base, pilosinine, $C_9H_{12}O_2N_2$. A similar degradation occurs when the alkaloid is heated with water or

dilute alkali at 140° for 10 hours (116, 117). When pilosine is oxidized with nitric acid, benzoic acid is formed (116).

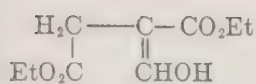
Pilosinine is a monoacidic base, and is optically active, the rotatory power falling rapidly in aqueous solution. It gives no color with diazo-benzenesulfonic acid and does not immediately decolorize permanganate. In its physical and chemical properties it closely resembles pilocarpine and isopilocarpine, and accordingly Pyman (46) proposed structures I and II for pilosine and pilosinine respectively, the alkaline degradation of pilosine being attributed to a reversed aldol condensation of a known type (177). On this basis, anhydropilosine has structure III. As pilosine



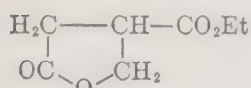
is not readily isomerized, it is regarded as being related stereochemically to isopilocarpine rather than to pilocarpine.

4. SYNTHESIS OF PILOSININE

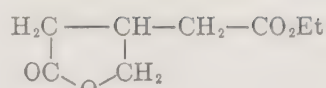
The Pyman structure (II) for pilosinine has been confirmed synthetically by N. A. and W. A. Preobrashenski and A. M. Poljakova (68). The synthesis follows similar lines to the same authors' synthesis of pilocarpine (Section II, 8). Reduction of ethyl formylsuccinate (IV) produces ethyl pilosinate (V), which is converted to ethyl homopilosinate (VI) by the Arndt-Eistert method, and thence through the diazo ketone into homopilosinylacetoxymethyl ketone (VII). When this substance is treated with copper acetate, formaldehyde, and ammonia at 100° for one hour, pilosinidine (VIII) is obtained, and this on methylation yields pilosinine (II). A modified synthesis was also described by the same authors, and more recently N. A. Dryamova, S. I. Zav'yalova, and N. A. Preobrashenski (72) have reported a third method. A similar synthesis of *dl*-isopropylpilosinine (IX) has been described by A. G. Natradze and E. E. Mikhlina (178).



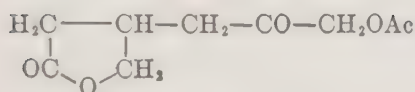
IV



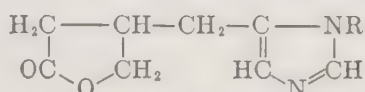
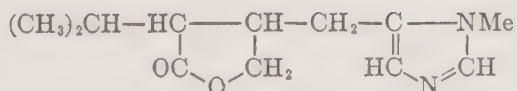
V



VI



VII

VIII, R = H
II, R = Me

IX

VI. Tables of Physical Constants of the Jaborandi Alkaloids, Their Derivatives and Degradation Products

Table 7. Melting and boiling points, and crystalline appearance.

Table 8. Solubilities of salts of the alkaloids.

Table 9. Optical rotatory powers.

Table 10. Refractive indices of crystalline salts.

TABLE 7
 MELTING AND BOILING POINTS, AND CRYSTALLINE APPEARANCE

Compound	M.p. [or b.p.] °C.	Crystal form (and crystalliza- tion solvent)	References
d-Pilocarpine	34	Long colorless needles	28, 39, 50,
	[260/5 mm.]		56, 81, 179
Argentonitrate [$B_2 \cdot AgNO_3$]	141 ^a	Crystalline (H ₂ O)	28
Aurichloride (+ H ₂ O)	ca. 100	Small yellow needles (dil. HCl)	28, 50, 107
(anhydrous)	117-130		28
	130	Crystals (AcOH)	50
	124-125		109
Auric chloride adduct [$B \cdot AuCl_3$]	167	Small yellow plates	50
	163 ^a		28
Chloroplatinate	218 ^a	Large orange plates (H ₂ O)	28, 36, 51,
			107
Compound with benzaldehyde bisulfite [$B \cdot C_7H_6O \cdot SO_2$]	105 (dec)		180
Compound with hematin		Blue black prisms	170
Compound with quinine-HCl	98-99		181
Ethiodide	114 ^a	Cubic crystals (EtOH-Et ₂ O)	28
Ethobromide	ca. 60		160
Hydrobromide	185 ^a		28
	178	Prismatic needles (EtOH)	50
	[128/0.02 mm.] ^b		184
Hydrochloride	200	Transparent prisms (EtOH)	81, 50
	205 ^a		182, 28
	208-210 (micro)		108
	[180/10 mm.] ^b		108
Hydroferricyanide (+ EtOH)		Pale yellow prisms (EtOH)	106
Hydroferrocyanide		White prismatic needles (H ₂ O)	106
Iodoargentate [$B \cdot HI \cdot AgI$]	169	Prisms (H ₂ O)	113
Iodobismuthate [$B_2 \cdot 2HI \cdot 3BiI_3$]		Ruby-red crystals	115
Iodobismuthate [$B_3 \cdot 3HI \cdot 4BiI_3$]		Orange-red crystals	115
Iodomercurate [$B_2 \cdot 2HI \cdot 3HgI_2$]		Yellow tablets (H ₂ O)	115
Mercurichloride [$B \cdot HgCl_2$]	145	Crystals (H ₂ O)	39
Methiodide		Oil	28
Methoaurichloride	103-104	Crystals (AcOH)	109
Methochloroplatinate	223-224	Orange rhombic plates	168, 109
Methopicate	142-143	Orange crystals (H ₂ O)	109
Nitrate	178 ^a	Large transparent prisms (H ₂ O)	28, 50, 59,
		Small needles (EtOH)	81
Pentaiodide [$B \cdot HI_5$]	135	Greenish-black cryst. (EtOH- H ₂ O)	183
Picrate	159-160 ^a	Long yellow needles (EtOH or H ₂ O)	48, 50, 109
	163-164 (dec)		126
	145-147		127
Picrolonate	200-205		129
Reineckate		Yellow or orange needles	120, 125
Salicylate	120	Needles or plates	50, 81
Styphnate	173-176 (dec)	Aggregates of long needles	126, 121
	183		128
Sulfate	132 ^a	Very small crystals (EtOH- Et ₂ O)	28, 81
	120		50
Tri-iodide [$B \cdot HI_3$]	148	Red cryst., metallic sheen, (EtOH-H ₂ O)	183
2:4:6-Trinitro- <i>m</i> -cresolate	188-189	Tufts of yellow-green needles	109, 124
Valerate			81
<i>Substitution products of pilocarpine</i>			
2-Bromo-, hydrochloride	240	Compact prisms (EtOH-HCl)	169

TABLE 7 (Continued)

Compound	M.p. [or b.p.] °C.	Crystal form (and crystalliza- tion solvent)	References
Dibromo-	95 ^a	Fine colorless prisms (EtOH-H ₂ O)	30, 39
Perbromide	106	Yellow-red needles (AcOH)	36
Dichloro-, hydrochloride		Lamellae	161
Nitro-	135-136	Prismatic needles (EtOH)	52
<i>Degradation products of pilocarpine</i>			
α-Anhydropilocarpic acid	243	Colorless lamellae (H ₂ O)	53
Hydrochloride	187	Crystals (EtOH)	53
Ethyl ester		Oil	53
Ethyl ester hydrochloride	122-125		53
Ethyl ester nitrate	165	Colorless needles (EtOH)	53
Bromo-	139	Crystals (EtOH)	53
β-Anhydropilocarpic acid	184	Prisms (H ₂ O)	53
Hydrochloride	142	Crystals (EtOH)	53
Ethyl ester	48	Large transparent plates	53
Ethyl ester nitrate	95		53
Bromocarpinic acid	209	Colorless prisms	39
Barium salt		Microcrystalline	36
Silver salt		White precipitate	36
γ-Chloropilocarpic acid			
Ethyl ester		Amorphous	53
Ethyl ester nitrate	136	Lamellae (EtOH)	53
Methyl ester	42-44	Transparent prisms (EtOH)	53
Methyl ester nitrate	157	Lamellae (EtOH)	53
Homopilocic acid methylanide	104	Long needles (EtOH)	168
Homopilocyl chloromethyl ketone	88.5-89.2		63
Nitropilocarpic acid	199	White crystals (EtOH)	52
Pilocarpoic acid anhydride	180	Thick prisms (EtOH-H ₂ O)	41
Pilomalic acid	145-146	Crystals (Et ₂ O)	41
<i>d</i> -Isopilocarpine	[261/10 mm.]	Long transparent oblique prisms	28, 50
Argentonitrate		Oil	28
Aurichloride	158-159 ^a	Fine yellow needles (dil. HCl)	28, 50, 109
Auric chloride adduct [B·AuCl ₃]	185-186 ^a	Yellow plates (H ₂ O)	28
	190		50
Chloroplatinate	226-227 ^a	Orange plates (H ₂ O)	28, 50
Hydrobromide	147 ^a	Hard prisms (EtOH-Et ₂ O)	28, 50
Hydrochloride (+ ½H ₂ O)	127 ^a	Plates (EtOH-Et ₂ O)	28, 50
(anhydrous)	159 ^a		28, 50
Mercurichloride [B·HgCl ₂]	164	Crystals (H ₂ O)	39
Methiodide	114 ^a	Prisms (EtOH)	28, 50
Methochloroplatinate	218 ^a	Orange cubes or rhombic plates	29, 33
	224-225	(dilute acid)	168
Methopierate	136 ^a	Orange needles (H ₂ O or EtOH)	29, 33
	119-120		109
Nitrate	159 ^a	Plates or prisms (EtOH or H ₂ O)	28, 50
Pierate	161 ^a	Long yellow needles (EtOH or H ₂ O)	28, 50
Salicylate	99	Plates (EtOH-Et ₂ O)	50
<i>Substitution products of isopilo- carpine</i>			
2-Bromo-, hydrochloride	201	Clusters of small needles (EtOH-Et ₂ O)	169
4(?) -Bromo-	164 ^a		30
Bromo-, perbromide	123	Crystals (EtOH-EtOAc)	41

TABLE 7 (Continued)

Compound	M.p. [or b.p.] °C.	Crystal form (and crystalliza- tion solvent)	References
Dibromo-	135 ^a	Rectangular prisms (EtOH)	30
Perbromide	165 ^a	Long yellow-brown needles (AcOH)	30
Nitro-	93-94	Colorless prisms (EtOH)	52
<i>Degradation products of isopilocarpine</i>			
5- <i>n</i> -Amyl-1-methylimidazole	[150-160/10 mm.]	Oil	33
Chloroplatinate	198	Light brown tablets or flakes (EtOH-HCl)	33, 171
Pierate	134	Yellow plates (C ₆ H ₆ or MeOH-	33
	125.5-128	H ₂ O)	171
γ-Chloroisopilocarpic acid			
Ethyl ester		Oil	53
Ethyl ester nitrate	95	Aggregated crystals (EtOH)	53
Methyl ester		Oil	53
Methyl ester nitrate	ca. 100	Crystals (EtOH)	53
Dibromoisopilocarpic acid	120-122 (dec)	Fine needles (dil. AcOH)	40
Barium salt		Needles (H ₂ O)	40
Dibromoisopilocarpinic acid	235 ^a (dec)	Rectangular prisms (90 % EtOH)	30
	224 (dec)	Needles	39, 40
α-Ethyltricarballic acid	157 ^a	Hard prisms (Et ₂ O or H ₂ O)	31
Homoisopilocipic acid	[235-237/20 mm.]	Liquid	31
Ethyl ester	[310-312; 210/10 mm.]	Liquid	31
Methylamide	53	Small prisms (EtOH-H ₂ O)	168
"Diamide" ^c	208 ^a	Prisms (H ₂ O)	31, 33
"Isopilocarpine anil"			
Nitrate	162	Colorless plates (acetone or EtOH)	54
Hydrochloride (+H ₂ O)	135	White prisms (acetone)	54
Isopilocarpic acid			
Chloroplatinate	180	Wart-like crystals (H ₂ O)	39
Isopilocarpinolactone (+H ₂ O)	80-83 ^a	Rectangular prisms (H ₂ O)	30
Isopilocarpoic acid	150	Colorless needles (H ₂ O)	41
Diethyl ester chloroplatinate	200	Small leaflets (H ₂ O)	41
Isopilocipic acid	104 ^a	Silky plates (C ₆ H ₆)	29, 31
Strychnine salt	120 ^a	Rosettes of crystals (EtOH- Et ₂ O)	31
Amyl ester	[192/25 mm.]	Yellow oil	38
Anilide	110 ^a	Colorless pearly plates (Et ₂ O)	31
Ethyl ester	[299]	Straw-colored mobile liquid	29
Methyl ester	[275/757 mm.]	Colorless liquid	31
	[155-160/10 mm.]		
"Diamide" ^c	160 ^a	Crystals (EtOH)	31
Isopilocipinic acid	98	Pearly plates (Et ₂ O-ligroin)	30
Ethyl ester	[262/10 mm.]	Thick straw-colored oil	30
Pilocarpidine			
Aurichloride	124-125 ^a	Prisms or needles (AcOH or 15 % HCl)	165, 164, 28, 109
Chloroplatinate (+4H ₂ O)	88-89 ^a	Yellow needles or flakes (H ₂ O)	28
	100		165
(+2H ₂ O)		Orange yellow plates	26
(anhydrous)	187 ^a		28, 165
Nitrate	137 ^a	Prismatic needles	28, 109, 59, 108

TABLE 7 (Continued)

Compound	M.p. [or b.p.] °C.	Crystal form (and crystalliza- tion solvent)	References
2:4:6-Trinitro- <i>m</i> -cresolate	149–150	Crystals (EtOH-H ₂ O)	109
Di-iodo-	192		172
2-Iodo-	161	Fine needles (H ₂ O)	172
Isopilocarpidine			
Nitrate	109–111	Crystals (EtOH)	109
Pilosine	187 ^a	Large colorless plates (EtOH)	46
	184–185 ^a	Colorless prisms or needles (EtOH or H ₂ O)	116
Aurichloride	143–144	Golden wedge-shaped plates (AcOH)	46
Chloroplatinate (+5H ₂ O)		Plates (EtOH-H ₂ O)	116
Hydrochloride		Colorless prisms (EtOH)	116
Hydrogen tartrate	135–136 ^a	Prismatic crystals (EtOH)	46
Methiodide		Yellow prisms (H ₂ O)	116
Sulfate	194–195 ^a	Clusters of plates (EtOH)	46, 116
<i>O</i> -Benzoyl, chloroplatinate		Granules (EtOH)	116
Potassium salt ^c		Long needles (H ₂ O)	116
Anhydropilosine	133–134 ^a	Colorless rods (EtOAc)	46
Hydrogen oxalate	153–154 ^a	Clusters of flat needles (EtOH)	46, 117
Nitrate	153–154 ^a	Tabular prisms (H ₂ O)	46
	151.7–153.7	Plates (MeOH)	117
Sulfate	174 ^a	Clusters of prisms (EtOH)	46
Pilosinine	78–79 ^a	Broad needles or plates (EtOAc)	46
	[300/35 mm.]		
Chloroplatinate		Plates (60% EtOH)	117
Hydrochloride	218–219 ^a	Prisms (H ₂ O or EtOH)	46
Nitrate	165–167 ^a	Colorless prisms (H ₂ O)	46, 117
Neopilocarpine	39–40 ^a		48
Hydrochloride	177 ^a	Large prisms (acetone-H ₂ O or acetone-EtOH)	48
Nitrate	94–95 ^a	Rosettes of needles (EtOH)	48
Picrate	117–119 ^a	Fine needles (EtOH)	48
Isonopilocarpine			
Nitrate	105–106 ^a	Prisms (EtOH)	48
Picrate	125–126 ^a	Prismatic needles (EtOH)	48
Pseudojaborine		Colorless sirup	49
Hydrochloride	220	Small prisms	49
Nitrate	158	Large thin plates (EtOH)	49
Pseudopilocarpine			
Hydrochloride	198–199	Small prisms	49
Nitrate	142	Small needles (EtOH)	49

^a Corrected.^b Sublimes.^c Derivative of the related hydroxy carboxylic acid, formed by opening of the lactone ring.

TABLE 8
SOLUBILITIES OF SALTS OF THE ALKALOIDS

Salt	Solvent	Temperature °C.	Solubility, g./100 g. solvent	References
Pilocarpine hydrochloride	Water	18	250	50
	95% EtOH	18	9.6	50
Pilocarpine nitrate	Water	20	15.6	28
	Water	18	14.4	50
	95% EtOH	18	0.68	50
	100% EtOH	20	0.37	28
Isopilocarpine nitrate	Water	19	11.9	28
	Water	18	12.4	50
	95% EtOH	18	0.74	50
	100% EtOH	20	0.28	28
Pilocarpidine nitrate	Water	15	50	28
	100% EtOH	15	1.23	28

TABLE 9
OPTICAL ROTATORY POWERS

Compound	Solvent	$[\alpha]^a$	Concn.	Temp., °C.	Ref.
Pilocarpine		+100.5°	1.064 → 19.83	—	28
	Water	+106°	2.0	18	50
	CHCl ₃	+106°	—	—	56
		+127°	—	—	179
	EtOH	+100°	2.09	—	56
Ethiodide		+65.2°	4.158	—	28
Hydrobromide		+77°	10.058	—	28
		+76°	2.0	18	50
Hydrochloride		+91.7°	9.924		28
	Water	+91.0°	2.0	18	50
Nitrate	Water	+82.9°	9.572		28
		+82.2	2.0	18	50
Salicylate		+62.5°	—	—	50
Sulphate	Water	+84.7°	7.318	—	28
		+85°	—	18	50
2-Bromopilocarpine hydrochloride	Water	+81.9° ₇₆₃₀	—	18	169
Dibromopilocarpine	EtOH	+43.6°	3.444	15	30
		+31.9°	2.19	18	39
Nitropilocarpine	CHCl ₃	+104°	5.0	—	52
	EtOH	+66°	1.25	—	52
	EtOH + HCl	+50°	—	—	52
	Aq. H ₂ SO ₄	+40°	5.0	—	52
	EtOH + H ₂ SO ₄	+34°	5.0	—	52
<i>Degradation products of pilocarpine</i>					
α -Anhydropilocarpic acid	Water	-19°	—	—	53
Ethyl ester nitrate	Water	+3.4°	—	—	53
	EtOH	-9.0°	—	—	53
β -Anhydropilocarpic acid	Water	+42°	1.5	—	53
Ethyl ester nitrate	Water	-28°	—	—	53
Bromocarpinic acid	EtOH	-90.5°	6.12	—	39
γ -Chloropilocarpic acid					
Ethyl ester	EtOH	+29.2°	—	—	53
		+37.0°	—	—	56
Ethyl ester nitrate	EtOH	+23.4°	2.5	—	53
Methyl ester	MeOH	+32.6°	6.0	—	53
Methyl ester nitrate	Water	+20°	—	—	53
Homopilopic methyl- amide	C ₂ H ₂ Cl ₄	+103.7° ₆₃₃₀	3.47	15	168
		+127.7° ₅₇₃₀	3.47	15	168
		+147.0° ₅₄₆₀	3.47	15	168
		+252.9° ₄₃₆₀	3.47	15	168

TABLE 9 (Continued)

Compound	Solvent	$[\alpha]^a$	Concn.	Temp., °C.	Ref.
Nitropilocarpic acid					
Barium salt	Water	+23°	3.335	15	52
Sodium salt	EtOH	+54°	—	—	52, 56
	Water	+35°	—	—	52, 56
Pilomalic acid	Water	-11.7°	9.225	—	41
Isopilocarpine		+42.8°	6.555 → 11.652	—	28
	Water	+50°	2.0	18	50
Hydrobromide		+32.8°	2.288	—	28
		+32.6°	—	—	50
Hydrochloride		+38.8°	4.974	—	28
		+37.3°	2.0	18	50
Methiodide		+30.4°	2.734	—	28
	Water	+26°	—	18	50
Nitrate		+35.68°	6.586	—	28
	Water	+38.5°	2.0	18	50
Dibromoisopilocarpine	Acetone	0°	6.0	—	30
Nitroisopilocarpine	EtOH	-8.0°	—	—	52
	CHCl ₃	-14°	—	—	52
	Aq. H ₂ SO ₄	0°	—	—	52
<i>Degradation products of isopilocarpine</i>					
γ-Chloroisopilocarpic acid					
Ethyl ester	EtOH	-3.0°	—	—	56
Ethyl ester nitrate	Water	0°	—	—	53
Methyl ester	EtOH	-7.5°	—	—	53
Methyl ester nitrate	MeOH	-5.6°	3.47	—	53
Dibromoisopilocarpinic acid	EtOH	+24.4°	6.544	16	30
Homoisopilocarpic acid	Water	+45.4°	3.524	21	31
	Aq. alkali	+5.9°	2.82	21	31
"Diamide" ^b		+21.4°	0.934		31
Methylamide	C ₂ H ₂ Cl ₄	+74.5° ₆₃₃₀	3.19	15	168
		+93.9° ₅₇₈₀	3.19	15	168
		+104.9° ₅₄₆₀	3.19	15	168
		+173.5° ₄₃₆₀	3.19	15	168
"Isopilocarpine anil" nitrate	Water	+21.2°	2.5	—	54
Isopilocarpinolactone	EtOH	-51.9°	4.046	16	30
Isopilocarpic acid	Water	+36.1°	3.324	15	29, 31
	Aq. alkali	+3.2°	9.5	17	29, 31
Ethyl ester	None	+39.8°	—	15	29
Barium salt ^b	Water	+6.1°	3.512	15	31
Isopilocarpinic acid	EtOH-H ₂ O	-13.6°	5.9	16	30

TABLE 9 (Continued)

Compound	Solvent	$[\alpha]^a$	Concn.	Temp., °C.	Ref.
Nitroisopilocarpic acid, sodium salt	Water	+50°	—	—	52
	EtOH	+47°	—	—	52
Pilocarpidine	Water	+81.3°	1.5374	—	28
Hydrochloride	Water	+72°	6.33	16	165
Nitrate		+73.2°	7.104	—	28
Pilosine	EtOH	+39.9°	0.827	—	46
	100% EtOH	+24.0°	1.014	20	116
	CHCl ₃	+40.2°	1.168	—	46
Hydrochloride	Water	+15.4°	1.212	22	116
Hydrogen tartrate		+24.2°	3.838	—	46
Sulfate	Water	+21.0°	4.454	—	46
Anhydropilosine	95% EtOH	+66.2°	3.571	—	46
Hydrogen oxalate	Water	-17.8°	4.093	—	46
Nitrate	Water	-18.1°	3.806	—	46
		-18.0°	3.517	—	117
Sulfate	Water	-17.6°	4.064	—	46
Pilosinine	Water	+14.2°	4.062	—	46
(after 24 hours)	Water	+9.8°	4.062	—	46
(after 48 hours)		+7.8°	4.062	—	46
(after 5 days)		+3.1°	4.062	—	46
Nitrate	Water	+4.3°	8.412	—	46
		+4.3°	8.465	—	117
Neopilocarpine					
Hydrochloride	Water	+66.4°	4.116	—	48

^a Specific rotations are for sodium light, unless another wavelength is indicated by subscript figures.

^b Derivative of the related hydroxy-dicarboxylic acid, formed by opening the lactone ring.

TABLE 10
REFRACTIVE INDICES OF CRYSTALLINE SALTS (132)

Salt	Refractive indices	
Pilocarpine borate	1.51	1.52
hydrobromide	1.63	1.55
hydrochloride	1.61	1.535
nitrate	1.60	1.55
salicylate	1.61	1.54
sulfate	1.55	1.615
valerate	1.55	1.51
Pilocarpidine nitrate	1.605	1.55

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CHAPTER 21

The Chemistry of Solanum and Veratrum Alkaloids

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	<i>Page</i>
I. Introduction.	248
II. Solanum Alkaloids	249
1. Glycosides—The Sugar Portion of the Glycoalkaloids.	249
a. Solanine	250
b. Solasonine	251
c. Demissine.	252
d. Solamargine.	252
e. Solasodamine	252
f. Tomatine.	252
g. Less-known Glycoalkaloids	253
2. Alkamines.	253
a. Solanidine and Demissidine.	253
b. Solasodine	258
c. Tomatidine.	267
d. Solanocapsine.	268
e. Less-known Alkamines	269
III. Veratrum Alkaloids.	270
1. Glycosides.	271
a. Veratrosine.	271
b. Pseudojervine.	272
2. Esters.	272
a. Cevadine.	272
b. Veratridine	273
c. Protoveratridine.	274
d. Germerine	274
e. Germidine	275
f. Germitrine	275
g. Protoveratrine.	275
h. Neogermitrine (Alkaloid A).	276
i. Alkaloids from <i>Zygadenus venenosus</i>	276
j. Escholerine.	277
3. Alkamines	277
a. Rubijervine.	277
b. Isorubijervine.	280
c. Veratramine.	282

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	<i>Page</i>
d. Jervine.	290
e. Cevagenine.	297
f. Cevine.	297
g. Germine.	306
h. Protoverine.	306
i. Zygadenine.	308
IV. References	309

I. Introduction

Many *Solanum* species contain alkaloidal glycosides which on removal of the sugar residue by hydrolysis yield alkamines with 27 carbon atoms. A number of the same alkamines have been also isolated along with their glycosides, but since no particular precautions to prevent enzymatic hydrolyses have been taken, it is not always certain that the alkamines are primary plant constituents. The alkamine solanocapsine has only been found as such, and it has not been possible to isolate its glycoside even under conditions designed to circumvent its hydrolysis.

The more common and more exhaustively investigated alkamines of the *Solanum* group on selenium dehydrogenation have yielded the typical steroid dehydrogenation product, namely γ -methyleclopentenophenanthrene. The nitrogen in these degradations appears in the form of 2-ethyl-5-methylpyridine. These dehydrogenation products indicate a very close structural relation to the steroids. In fact, the physical and chemical properties of the *Solanum* alkamines and their derivatives display a remarkable similarity to their steroid counterparts, so that in many cases it has been possible to write satisfactory structural formulas by analogy. Finally, it has been possible to relate some of the more common alkamines experimentally with known steroids, so that the term "steroid" alkaloids has a firm factual basis. Similar alkamines with 27 carbon atoms have been obtained from a number of *Veratrum*, *Sabadilla*, and *Zygadenus* species in which they occur as glycosides, as esters with known low-molecular-weight acids, or in the free state.

Those *Veratrum* alkamines that have been subjected to selenium dehydrogenation have yielded the typical basic dehydrogenation product, namely 2-ethyl-5-methylpyridine; the γ -methyleclopentenophenanthrene was however not obtained. Of the *Veratrum* alkamines rubijervine and isorubijervine could be correlated to *Solanum* alkaloids by other methods. Nevertheless, most of the compounds of this group exhibit properties and reactions which indicate a close relation to steroids and particularly to the steroid alkaloids, although their structures are not known in detail. It is therefore convenient to deal with the *Solanum* and *Veratrum* alkaloids as one group. General references and reviews are given at the end of the chapter.

II. Solanum Alkaloids

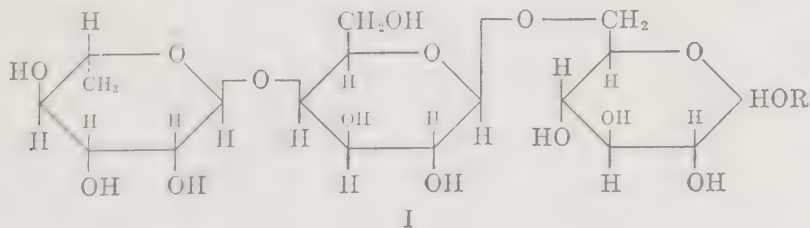
1. GLYCOSIDES—THE SUGAR PORTION OF THE GLYCOALKALOIDS

The known glycoalkaloids, their corresponding alkamines, and their sugar moiety are given in Table 1.

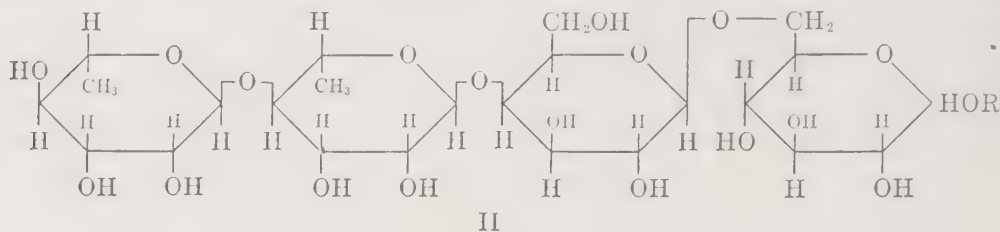
TABLE 1

Glycoalkaloid	Aglycone	Sugar
Solanine (Solanine t, Solatunine) $C_{45}H_{73}O_{15}N$	Solanidine (Solatubine) $C_{27}H_{43}ON$	L-Rhamnosido-D-galacto- sido-D-glucose
Demissine (Solanine d) $C_{50}H_{83}O_{20}N$	Demissidine (Solanidan-3 β -ol) $C_{27}H_{45}ON$	Tetrasaccharide of 1 mole D-xylose, 1 mole D-galactose and 2 moles D-glucose
Solasodamine $C_{51}H_{87}O_{20}N$	Solasodine (Solanidine s, Solancarpidine, Pura- puridine) $C_{27}H_{43}O_2N$	L-Rhamnosido-L-rhamno- sido-D-galactosido-D- glucose
Solasonine (Solanine s, Solancarpine, Purapurine) $C_{45}H_{73}O_{16}N$		L-Rhamnosido-D-galacto- sido-D-glucose
Solamargine $C_{45}H_{73}O_{16}N$		L-Rhamnosido-L-rhamno- sido-D-glucose
Solauricine $C_{45}H_{73}O_{16}N$	Solauricidine $C_{27}H_{43}O_2N$	L-Rhamnosido-D-galacto- sido-D-glucose
Solangustine $C_{33}H_{53}O_7N$	Solangustidine $C_{27}H_{43}O_2N$	D-Glucose
Alkaloid from <i>S.</i> <i>panduracforme</i> $C_{45}H_{73}O_{16}N(?)$	Aglycone $C_{27}H_{43}O_2N$ isomeric with Solasodine	L-Rhamnosido-D-galacto- sido-D-glucose
Tomatine $C_{50}H_{83}O_{21}N$	Tomatidine $C_{27}H_{45}O_2N$	Tetrasaccharide of 1 mole D-xylose, 1 mole D-galactose and 2 moles D-glucose

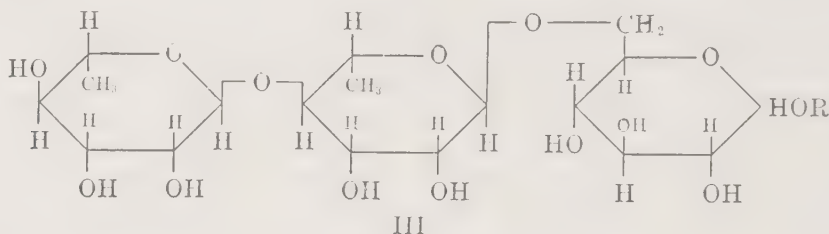
The two most widely distributed glycoalkaloids, solanine and solasonine, as well as the less-known solauricine and the alkaloid from *Solanum panduracforme* Drege contain as sugar component a trisaccharide, L-rhamnosido-D-galactosido-D-glucose (I), for which the name solanose has been proposed (11, 12, 13, 14, 38, 60, 62).



The recently isolated solasodamine contains as sugar compound a tetrasaccharide consisting of two moles of L-rhamnose and one each of D-galactose and D-glucose, probably represented by II (12). A trisaccharide not identical with solanose has been obtained from solamargine.



It is an L-rhamnosido-L-rhamnosido-D-glucoside of probable structure III (11, 12, 13).



In the above three formulas the group R represents the alkaline component. The order of attachment of the monosaccharide components was determined by partial and progressive hydrolysis. The pyranose type and the position of coupling of the sugars was determined from the periodic acid oxidation, but the complete structures are not known with certainty.

A tetrasaccharide consisting of one mole each of D-xylose and of D-galactose, and two of D-glucose, in which the order of combination is unknown, forms the sugar component of demissine (31) and of tomatine (35).

Finally, a monosaccharide, solangustine, which is a D-glucoside, has been described. It is however possible that this is a product of partial hydrolysis (58).

It should be noted that the sugar components of many glycoalkaloids that have been described as "solanine" have not been determined (36, 61), and a reinvestigation using modern techniques, as for example paper chromatography, is necessary to determine the proper order and the type and number of monosaccharides.

a. *Solanine* (*Solanine t*, *Solatunine*). The names solanine t and solatunine have been suggested to indicate the known differences between the alkaloids of *Solanum tuberosum* L. and *S. sodomaeum* L. Since however the name solasonine for the alkaloid from the latter has now received

general acceptance, it is preferable to retain the older name of solanine for the glycoalkaloid from *S. tuberosum*.

Solanine was first found by Desfosses (22) in *S. nigrum* L. in 1820, and Baup (3) a little later isolated it from potatoes (*S. tuberosum*). Potato sprouts are particularly rich in solanine and serve as a convenient source of this alkaloid. Solanine is accompanied in potato sprouts by its aglycone, solanidine (19). The distribution of both alkaloids in the various parts of the potato and the influence of various factors on the alkaloid content have been exhaustively studied (34). The following plants have been recorded as containing solanine (61), but the older work requires confirmation since the identification in many instances was superficial and therefore other glycosides are a possibility: *S. aculeatissimum* Jacq., *S. asperum* Vahl, *S. bacciferum*, *S. caavurana* Vell., *S. carolinense* L., *S. dulcamara* L., *S. grandiflorum* Ruiz and Pav., *S. mammosum* L., *S. paniculatum* L., *S. peckoltii* (?), *S. tomatillo* Phil., *S. verbascifolium* L., *S. villosum* Willd., *Capsicum annuum* L., *Physoclaina orientalis* G. Don, and *Lycopersicum esculentum* (L.) Mill.

Isolation. The fresh crushed potato sprouts are allowed to remain for 48 hours with twice their weight of 2% acetic acid. The acid solution is separated with the aid of a centrifuge, filtered with a little celite, and rendered distinctly alkaline by the addition of ammonia. After 24 hours the precipitate is separated by filtration, washed, and dried. The admixed solanidine is separated by exhaustive ether extraction and may be obtained in impure form by evaporation of the ether. The ether-insoluble portion is extracted with hot 80% ethanol and, upon concentrating and cooling the extract, the crude solanine separates. It may be recrystallized from 80% ethanol or from dioxane (39, 56). As thus purified it melts at 285° and has $[\alpha]_D - 42^\circ$ (dilute hydrochloric acid), -56.5° (pyridine), -60° (pyridine) (31, 62).

Solanine hydrochloride melts at 212° (dec.). The acetyl derivative, which melts at 204–205° and has $[\alpha]_D - 35^\circ$, when treated with hydrobromic acid in acetic acid yields (1) tetraacetylramnose, (2) an acetyl solanidine-*D*-galactosido-*D*-glucoside, and (3) an acetyl solanidine-*D*-glucoside melting at 115–120°, $[\alpha]_D - 8.0^\circ$ (38, 62). When solanine is hydrolyzed in aqueous or alcoholic solution with hydrochloric acid, it yields L-ramnose, *D*-galactose, and *D*-glucose as well as solanidine, which, dependent upon the reaction conditions, is accompanied by varying amounts of its dehydration product, namely, $\Delta^{3,5}$ -solanidene (solanthrene) (56).

b. Solasonine (Solanine s, Solancarpine, Purapurine). In 1905 Oddo (37) established that the "solanine" from the berries of *S. sodomum* was not identical with that of *S. tuberosum*. It was subsequently shown that this alkaloid, which was first termed solanine s and then solasonine to distinguish it from the solanine t of *S. tuberosum*, was identical with the glycoalkaloid from *S. xanthocarpum* Schrad. & Wendl. (solancarpine)

(8, 9), from *S. aviculare* Forst. (purpurine) (8), and from *S. torvum* Sw. (29).

Isolation. Solasonine may be isolated from the dried berries of *S. sodomium* by alcohol extraction or from the expressed juice of the green mashed berries. In the first case the alcohol-free extract is extracted with hot 2% acetic acid and the hot solution basified with ammonia. From the juice of the berries the alkaloid can be precipitated by passing gaseous ammonia into the hot solution. It is conveniently purified by reprecipitating it from its acetic acid solution with ammonia (17).

Properties. Solasonine, $C_{45}H_{73}O_{16}N$, crystallizes from methanol, dilute ethanol, or dioxane with solvent of crystallization; m.p. 285°; $[\alpha]_D - 53^\circ$ (ethanol); picrate, m.p. 197°; picrolonate, m.p. 231°. Acid hydrolysis yields L-rhamnose, D-galactose, D-glucose and the aglycone, solasodine, $C_{27}H_{43}O_2N$, which is generally accompanied by its dehydration product, $\Delta^{3,5}$ -solasodiene (solanosodine) (4, 8, 9, 10, 17, 29, 37, 38, 42, 43, 46).

c. Demissine. In the leaves of potato species (*S. demissum* Lindl.) that are resistant to the attacks of the larvae of the potato beetle (*Leptinotarsa decemlineata* Say) Kuhn and Löw found a glycoalkaloid to the extent of 4.7 g. per kilogram of fresh leaves which is responsible for this resistance to attack. The alkaloid was isolated by extracting the dried leaves with dilute acetic acid and precipitating it from the extract with ammonia (30, 31).

Properties. Demissine, $C_{50}H_{83}O_{20}N$, melts at 305–308° when recrystallized from methanol or ethanol; $[\alpha]_D - 20^\circ$ (pyridine). Acid hydrolysis yields one mole each of D-xylose and D-galactose and two of D-glucose as well as demissidine, $C_{27}H_{46}ON$ which proved to be solanidan-3 β -ol (31).

d. Solamargine. Briggs (11, 12, 13) isolated this glycoalkaloid, $C_{45}H_{73}O_{15}N$, from *S. marginatum* L. Complete hydrolysis in dilute ethanolic hydrochloric acid yielded two moles of L-rhamnose, one mole of D-glucose, and the aglycone solasodine, $C_{27}H_{43}O_2N$. Partial hydrolysis with 3% aqueous hydrochloric acid generates solasodine-D-glucoside, which on hydrolysis with 10% hydrochloric acid is split into D-glucose and solasodine. Solamargine therefore is solasodine-L-rhamnosido-L-rhamnosido-D-glucoside.

e. Solasodamine. Briggs (12) has isolated a tetrasaccharide of solasodine, $C_{51}H_{83}O_{20}N$, from the berries of *S. sodomium*, *S. auriculatum* Ait., *S. marginatum*, and *S. aviculare* under conditions such that enzymatic hydrolysis was prevented. Partial hydrolysis results in a solasodine-D-galactosido-D-glucoside and therefore solasodamine is probably solasodine-L-rhamnosido-L-rhamnosido-D-galactosido-D-glucoside, that is, solasonine-L-rhamnoside.

f. Tomatine. This alkaloid occurs in certain tomato species which, because of their antibiotic, fungistatic, and insecticidal action, are of

interest similar to that of *S. demissum*. It was present up to an amount of 5% in the dried leaves of the following tomato species; *Lycopersicum pimpinellifolium* Mill. (*S. racemigerum* Zodda (?)), *L. esculentum* and its several horticultural varieties, *L. peruvianum* Mill., *L. peruvianum chutatum* (?), and *L. hirsutum* H.B. & K. (18, 27, 32) cf. also F. Galinovsky and A. Wagner, *Monatsh. Chem.* **82**, 1123 (1951).

Isolation. The leaves of the tomato plants are extracted with ethanol, the solvent-free extract boiled with water, and the clarified solution precipitated with ammonia. The crude alkaloid thus obtained is reprecipitated from acid solution and then recrystallized from dilute ethanol or from dioxane (27).

Properties. Tomatine, $C_{50}H_{83}O_{21}N$, crystallizes from 80% dioxane or from 70% ethanol in colorless groups of needles which melt at 263 to 267° with decomposition, the exact temperature depending upon the rate of heating (18, 27, 32). Acid hydrolysis liberates one mole each of D-xylose and D-galactose and two of D-glucose (35).

g. Less-known Glycoalkaloids. *Solauricine*, $C_{45}H_{73}O_{16}N$, was obtained from *S. auriculatum* and, when crystallized from dilute ethanol or from dioxane, it melted at 270°; picrate, m.p. 185°; picrolonate, m.p. 232°. Acid hydrolysis yielded L-rhamnose, D-galactose, D-glucose, and the aglycone solauricidine, $C_{27}H_{43}O_2N$, which though very similar to solasodine does not appear to be identical with it (1, 5, 14).

The glycoalkaloid from *S. panduraeforme* is very similar to solauricine and yields the same sugars on hydrolysis together with an aglycone, $C_{27}H_{43}O_2N$, probably not identical with solasodine (60).

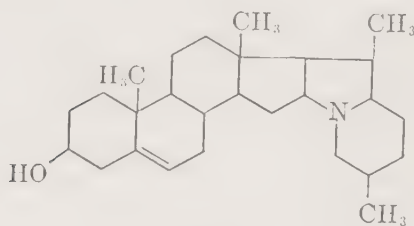
Finally, the glycoalkaloid *solanangustine*, $C_{33}H_{53}O_7N \cdot H_2O$, m.p. 235° (from hot amyl alcohol), from *S. pulverulentum* Pers. (*S. angustifolium* Ruiz & Pav.), has been known for a long time. It yields a crystalline sulfate and on energetic hydrolysis it generates D-glucose and solangustidine, $C_{27}H_{43}O_2N$, isomeric with solasodine. Since strong acid solution was used during the isolation of solangustine, it is not improbable that it is the product of partial hydrolysis of a higher saccharide (41, 58).

2. ALKAMINES

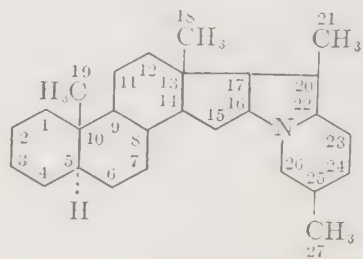
a. Solanidine (Solanidine t, Solatubine) and Demissidine. Solanidine occurs as such in potato sprouts (19) and is conveniently prepared by the hydrolysis of solanine. The yield of by-product $\Delta^{3,5}$ -solanidiene in this hydrolysis is somewhat reduced if the reaction is done in alcoholic solution. The synonyms had been used to differentiate the solanidine of *S. tuberosum* from the aglycone of the alkaloid of *S. sodomaeum*, but since the latter is now known as solasodine the synonyms are no longer necessary.

The elucidation of the structure of solanidine as IV (21, 39) followed the degradative work and was confirmed by a partial synthesis.

NOMENCLATURE. The relationships in the steroids which find many counterparts in numerous solanidine derivatives suggest a rational nomenclature based on that of the steroids. The oxygen-free saturated compound V serves as the basic skeleton and is termed solanidane. This terminology will be used here, adopting the latest principles of steroid nomenclature (63). Instead of the earlier terms *cis*-, *trans*-, and *allo*-, the letters α , β , and ξ will be used to indicate configuration in the same way that they are used in the steroid group.



IV



V

STRUCTURE AND REACTIONS. Solanidine, $C_{27}H_{43}ON$ (IV), has one basic tertiary nitrogen and one secondary hydroxyl as well as a double bond capable of being detected by catalytic hydrogenation. Solanidine is therefore hexacyclic. Its dissociation constant pK_B is 5.38 (11) and it forms stable well-crystallizing salts as well as a methiodide. The hydroxyl is readily esterifiable and a number of acyl derivatives are known.

Solanidine yields a sparingly soluble digitonide with digitonin and, since only 3β -hydroxy steroids yield such compounds, the inference that the hydroxyl is also in the 3β -position is mandatory.

HYDROGENATION, OXIDATION, AND DEHYDRATION. The relative positions of the hydroxyl and the double bond were determined by the following reactions, which are generally useful in other *Solanum* as well as *Veratrum* alkaloids. Solanidine on dehydrogenation with copper or by Oppenauer oxidation yields a ketone, $C_{27}H_{41}ON$, which on the basis of its UV-spectrum must be an α,β -unsaturated ketone. This ketone on reduction with sodium and ethanol or with aluminum isopropylate (Meerwein-Ponndorf) regenerates a mixture of epimeric alcohols which with trichloroacetic acid give the color reaction of Rosenheim, characteristic of α,β -unsaturated alcohols, and not given by solanidine. One of the epimers gives a sparingly soluble digitonide but is different from solanidine, and this indicates a shift of the double bond from its original 5,6-position to the 4,5-position during the formation of the ketone, a shift often encountered in many naturally occurring steroids. Solanidine therefore is a Δ^5 -solaniden-3-ol and the ketone obtained from it is Δ^4 -solaniden-3-one (VI). The α,β -unsaturated alcohols obtainable

from the ketone are Δ^4 -solaniden- 3β -ol (VII) and Δ^4 -solaniden- 3α -ol (VIII). The latter was obtainable in a nearly pure form from the mother liquors of the separation of the digitonide of the former (44, 45, 54).

Solanidine on hydrogenation in acetic acid in the presence of platinum oxide yields solanidan- 3β -ol (IX) in which the rings A and B are fused in the trans positions. Its epimer, solanidan- 3α -ol (XI) is obtainable by reacting the *p*-toluenesulfonate of IX with potassium acetate. The ketone X, obtainable from IX by Oppenauer oxidation also yields XI when it is reduced catalytically in acetic acid containing hydrogen bromide in the presence of platinum oxide (6, 23, 40, 45).

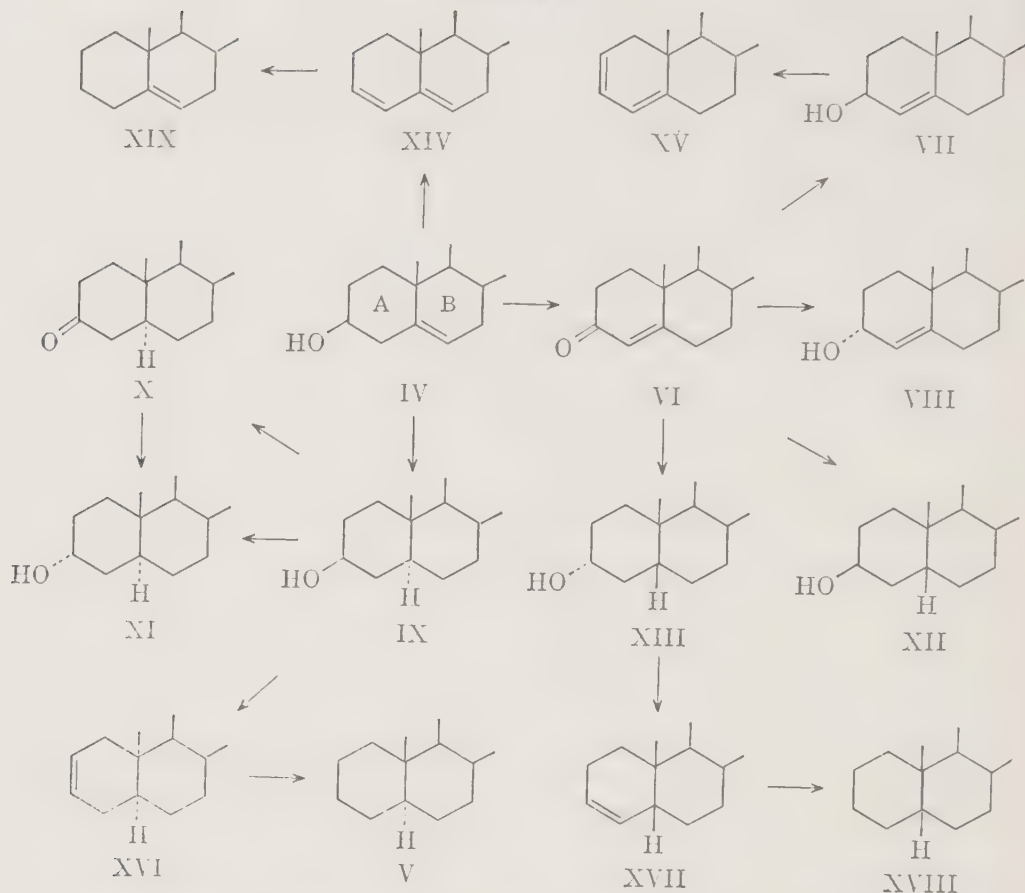
Two further dihydrosolanidines (solanidanols) with *cis*-junction of the A and B rings are formed when Δ^4 -solaniden-3-one is catalytically reduced in the presence of Raney nickel. The 5β -solanidan- 3α -ol (allosolanidan- 3α -ol) (XIII), which is obtained in larger amount, may be separated from the 5β -solanidan- 3β -ol (allosolanidan- 3β -ol) (XII), which forms a sparingly soluble digitonide (40).

A number of doubly unsaturated oxygen-free compounds are available as the result of dehydrating solanidine and its isomers. The most stable of these is $\Delta^{3,5}$ -solanidiene (XIV), which has been obtained as a by-product under the name solanthrene during the hydrolysis of solanine. The position of the double bonds in this diene follow from the study of its UV-spectrum and from a study of its optical rotation. The isomeric $\Delta^{2,4}$ -solanidiene is obtainable by the thermal decomposition of benzoyl- Δ^4 -solaniden- 3β -ol (6, 24, 45, 54, 55).

The $\Delta^{3,5}$ -solanidiene can be partially reduced over a palladium catalyst to a solanidene (XIX) in which the double bond is most probably at the 5,6-position. A different solanidene is obtained when water is eliminated from solanidan- 3β -ol (IX). The double bond in this material, which may prove to be a difficultly separable mixture, is either at the 2,3- or 3,4-position. Finally, another solanidene was obtained by the Clemmensen reduction of Δ^4 -solaniden-3-one (?) (VI). The double bond was assumed to be in the 4,5-position, but it may be in the 3,4-position, or the product may be a mixture. Catalytic reduction of the singly and doubly unsaturated compounds in all cases yields solanidane (V), the basic structure of the solanidine group, and the analogue of cholestane in the steroids (6, 40, 55).

The isomeric basic structure with *cis*-junction of the rings A and B, namely 5β -solanidane (XVIII) (formerly, allosolanidane) is obtainable by dehydration of 5β -solanidan- 3α -ol (XIII) to what is probably Δ^3 - 5β -solanidene (XVII) and reduction of the latter. Some of the above-mentioned interrelations are summarized in Table 2.

TABLE 2



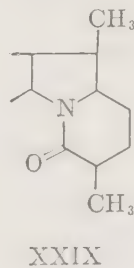
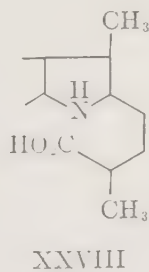
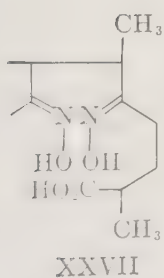
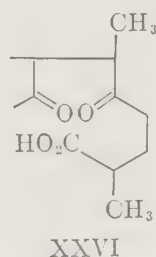
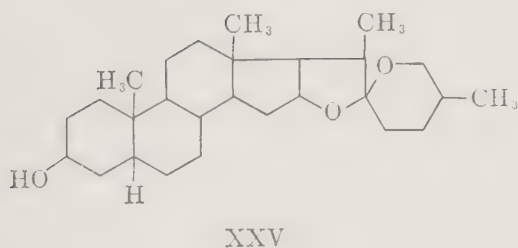
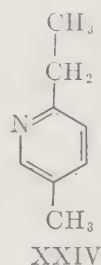
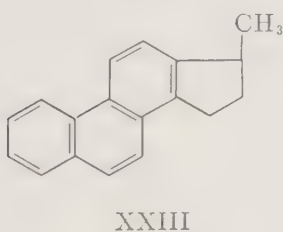
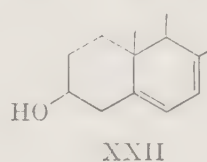
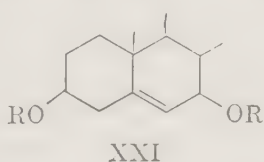
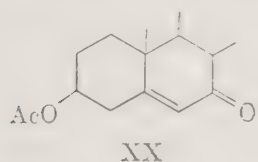
In addition to the parallelism of the above reactions with those in the steroids, there is a close correspondence in the optical rotation of similar derivatives, and even before the two classes of compounds were directly related their structures were for a large part considered to be identical (40). Experiments with monomolecular films led to the same conclusions (50).

Hydrogen peroxide and peracids react with solanidine acetate, with solanidan-3 β -ol, or with solanidane to yield *N*-oxides, which on treatment with sulfur dioxide regenerate the starting material. With one mole of perbenzoic acid, Δ^2 -solanidene yields an *N*-oxide but with two moles of the reagent it yields a 2,3-epoxide-*N*-oxide, which on treatment with sulfur dioxide generates a diol, probably solanidan-2,3-diol (15, 45, 57).

Chromic acid in acetic acid reacts with solanidine acetate in a manner analogous to the reaction of cholesterol acetate to give a 7-keto compound. The resultant 7-ketosolanidine acetate (XX) may be reduced to the corresponding 7-hydroxy compound (XXI) whose dibenzoate on thermal decomposition and hydrolysis of the pyrolyzate

affords 7-dehydrosolanidine ($\Delta^{5,7}$ -solanidien-3 β -ol) (XXII) (48), an analogue of 7-dehydrocholesterol.

The stability of the grouping of which the nitrogen is the core is remarkable. The quaternary ammonium bases available via the methiodide and reaction with fixed alkali or silver oxide lose methanol on heating and regenerate the starting material. It was also not possible to degrade solanidine or its derivatives with cyanogen bromide (23, 54).



DEHYDROGENATION. The definite determination of the skeletal structure of solanidine, and particularly that portion of the molecule which carries the nitrogen, was accomplished by dehydrogenation with selenium and identification of the products. Early attempts in this direction led to phenanthrene, chrysene, and pyridine (23) presumably because of too drastic conditions. Under so called normal conditions, that is tempera-

tures at which the sterols yield γ -methylecyclopentenophenanthrene (XXIII) solanidine yields the same product (42, 56) as well as 2-ethyl-5-methylpyridine (XXIV) (20, 21, 39). These fragments rendered it possible to arrive at the correct skeletal structure and to suggest formula IV for solanidine.

PARTIAL SYNTHESIS OF 5β -SOLANIDAN- 3β -OL FROM SARSASAPOGENIN. The close similarity of the skeletal structures of solanidine and sarsasapogenin (XXV) and the favorable position of functional groups in the latter made it possible to convert it into 5β -solanidan- 3β -ol (XII) which had already been prepared from solanidine (40, 59). The dioxime (XXVII) of sarsasapogenic acid (XXVI), obtainable from the genin by oxidation, on catalytic reduction yielded an aminocarboxylic acid (XXVIII) whose lactam (XXIX) on further and energetic catalytic reduction afforded XII. Not only do these results prove the correct structure of solanidine (IV), but the steric configuration of the greater part of the molecule is also established. There remains only to be determined the configuration of the asymmetric carbons 16, 17, 20, 22, and 25.

Demissidine, $C_{27}H_{45}ON$, the aglycone of demissine, was shown to be identical with solanidan- 3β -ol (IX), obtainable by the catalytic reduction of solanidine (31).

b. *Solasodine* (*Solanidine s*, *Solancarpidine*, *Purapuridine*). Solasodine is the aglycone of solasonine (solancarpine, purapurine), of solasodamine, and of solamargine, and is prepared from these by hydrolysis with 3% hydrochloric acid at 100° . The cooled reaction mixture deposits the sparingly soluble hydrochloride from which the free base may be regenerated. It is dimorphic but both forms melt at 198 – 200° (5).

The structure of solasodine has been determined to a large extent but not entirely. That (XXX) of L. H. Briggs will be used in the following discussion (15).

NOMENCLATURE. In analogy with the solanidine series it is possible to base the nomenclature on an oxygen-free saturated solasodane (XXXI) with *trans*-junction of rings A and B in conformity with present steroid naming.

STRUCTURE AND REACTIONS. Solasodine, $C_{27}H_{43}O_2N$, is a weaker base than solanidine and has pK_B 6.30 (11). One of the oxygen atoms is present as a secondary hydroxyl in position 3β as shown by the formation of a sparingly soluble digitonide and by the reactions to be described later. The function of the second oxygen was more difficult to determine. Since the alkaloid reacted as though it had two active hydrogens (46), it was originally assumed that a nonreactive, presumably tertiary, hydroxyl was also present. More recent investigations have shown how-

ever that the second active hydrogen is in the form of a secondary nitrogen and that the oxygen is present as a cyclic ether (15, 17).

One double bond is detectable by hydrogenation so that solasodine is hexacyclic. It yields well-crystallizing salts; however with methyl or ethyl iodide it does not react to form quaternary iodides but the hydriodide of solasodine (4, 5, 17).

The hydroxyl in the alkaloid is readily acylated with the formation of well-defined basic monoacyl derivatives. A diacetyl derivative may be obtained but not in crystalline condition. Nitrous acid generates an *N*-nitroso compound (15, 17, 46).

OXIDATION, HYDROGENATION, AND DEHYDRATION REACTIONS. Oppenauer oxidation as well as dehydrogenation with copper powder leads to the formation of an α,β -unsaturated ketone, namely, Δ^4 -solasoden-3-one, which on Meerwein-Ponndorf reduction affords a mixture of two epimeric Δ^4 -solasoden-3-ols, one of which forms a sparingly soluble digitonide. Neither of these is identical with solasodine and both give the positive Rosenheim reaction for α,β -unsaturated alcohols. These reactions are therefore analogous to those in the solanidine series (VI to VIII) and lead to the same conclusion, namely, that the double bond in solasodine is in the β,γ -position to the 3β -hydroxyl (17, 46, 49). In analogy with solanidine, it is possible to eliminate the elements of water from solasodine to yield a diene, also obtained as by-product during the hydrolysis of the alkaloid glycoside, and formerly named solanosodine. Its structure as $\Delta^{3,5}$ -solasodiene is confirmed by UV-spectra.

Hydrogenation in the presence of a palladium charcoal catalyst in ethanol or acetic acid yields a dihydro derivative, $C_{27}H_{45}O_2N$, which is formulated as solasodan- 3β -ol. Its basicity, pK_B 6.36 (11), is the same as solasodine and it behaves toward acylating agents, to ethyl iodide, and to nitrous acid, in the same way as its unsaturated precursor (15, 17, 49).

On the other hand, if the hydrogenation is effected in the presence of a platinum oxide catalyst in ethanol-acetic acid two moles of hydrogen are absorbed with the formation of a dihydrosolasodan- 3β -ol, $C_{27}H_{47}O_2N$. In this compound the saturation of the double bond as well as the hydrogenolysis of the oxide ring with the formation of a new hydroxyl has taken place, as also certain changes in the region of the nitrogen atom. This dihydro compound with a pK_B of 4.28 (11) is a stronger base than solasodine or than solanidine. With acetic anhydride it forms an *O,O',N*-triacetyl derivative and with methyl iodide it yields an *N*-methyl derivative. It still yields an *N*-nitroso compound (15, 16, 17, 28, 46).

A scission of the oxide ring without reduction of the double bond can be achieved by lithium aluminum hydride. The resultant dihydro-

TABLE 3
PROPERTIES OF SOLANIDINE AND ITS DERIVATIVES

Compound	Formula	M.p. °C.	$[\alpha]_D$	$[\alpha]_{H_g}$	Ref.
Solanidine (IV) ^a	C ₂₇ H ₄₃ ON	219			6, 19, 23, 42, 54, 55, 56 40, 55
Hydrochloride			-27.3° (CHCl ₃)		19
Methohydroxide		335	-28.5° (C ₂ H ₅ OH)		54, 55
Formylsolanidine	C ₂₃ H ₄₃ O ₂ N	285-286			54
Acetylolanidine	C ₂₉ H ₄₅ O ₂ N	280 (dec) 168-169 206-208 204 207			55 54 54 55 6
Acetylsolanidine N-oxide	C ₂₉ H ₄₅ O ₃ N	263-265	-32.5° (CHCl ₃)		40
Palmitylsolanidine	C ₄₃ H ₇₃ O ₂ N	83			45
Hydrochloride		225-226			54
Benzoylsolanidine	C ₃₄ H ₄₇ O ₂ N	214			54
Solanidine ozonide	C ₂₇ H ₄₃ O ₄ N	270 (dec)			6
Solanidan-3β-ol (Demissidine) ^a	C ₂₇ H ₄₅ ON	222			56
		219-220			6
		221	+20.6° (CHCl ₃)		23
		220			45
		216-218			40
Methiodide			+28.2° (CHCl ₃)		31
Solanidan-3β-ol-N-oxide	C ₂₇ H ₄₅ O ₂ N	280 (dec)			40
Hydrogen peroxide solanidan-3β-ol	C ₂₇ H ₄₅ ON	242-244			15
Acetylsolanidan-3β-ol	C ₂₉ H ₄₇ O ₂ N	178.5-179.5 (dec) 195 196			15 6
Palmitylsolanidan-3β-ol	C ₄₃ H ₇₅ O ₂ N		+16.5° (CHCl ₃)		40
Hydrochloride		225			6

p-Toluolsulfosolanidan-3 β -ol	C ₃₄ H ₅₁ O ₃ NS	169.5-170			40
Solanidan-3 α -ol (XI)	C ₂₇ H ₄₅ ON	211-212	+31.9° (CHCl ₃)		40
Acetylsolanidan-3 α -ol	C ₂₉ H ₄₇ O ₂ N	174-176	+21.9° (CHCl ₃)		40
5 β -Solanidan-3 β -ol (XII) (Allo-solanidan-3 β -ol) ^a	C ₂₇ H ₄₅ ON	216-217.5 216-218	+27.9° (CHCl ₃)		10 50
Acetyl-5 β -solanidan-3 β -ol	C ₂₉ H ₄₇ O ₂ N	140-141 144-146	+27.3° (CHCl ₃) +31.4° (CHCl ₃) +28° (CHCl ₃)		59 40 59
5 β -Solanidan-3 α -ol (XIII) (Allo-solanidan-3 α -ol)	C ₂₇ H ₄₅ ON	212-214	+34.5° (CHCl ₃)		40
Acetyl-5 β -solanidan-3 α -ol	C ₂₉ H ₄₇ O ₂ N	140-141.5	+45.2° (CHCl ₃)		40
Δ^4 -Solaniden-3-one (VI) ^{b,c}	C ₂₇ H ₄₁ ON	218 216			54 44
		213-216.5	+89.0° (CHCl ₃) +152° (CHCl ₃)		40 44, 45
Oxime		228			54
Semicarbazone		237			54
Diisnitroso- Δ^4 -solaniden-3-one	C ₂₉ H ₃₉ O ₃ N ₃	242			54
Δ^4 -Solaniden-3 β -ol (VII) ^{a,d}	C ₂₇ H ₄₃ O ₂ N	203-204 201	+91.5° (CHCl ₃)		44 45
Acetyl- Δ^4 -solaniden-3 β -ol ^d	C ₂₉ H ₄₅ O ₂ N	181-183			44
Benzoyl- Δ^4 -solaniden-3 β -ol	C ₃₄ H ₄₇ O ₂ N	199			45
Δ^4 -Solaniden-3 α -ol (VIII) ^d	C ₂₇ H ₄₃ ON	169-170			45
Solanidan-3-one (X) ^e	C ₂₇ H ₄₃ ON	214 210-212 237°	+116.4° (CHCl ₃) +48.9° (C ₆ H ₆) +31.9° (CHCl ₃)		45 45 40
Semicarbazone					45
$\Delta^{3,5}$ -Solanidiene (XIV) (Solan-threne) ^f	C ₂₇ H ₄₁ N	172 166-167 170			25 6, 54 55
Hydrochloride		above 300	-186° (CHCl ₃) -274.5° (CHCl ₃)		45 54

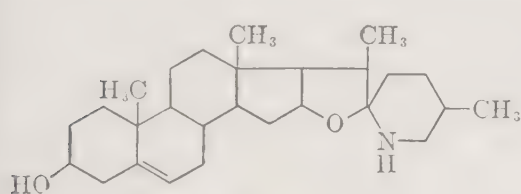
TABLE 3 (Continued)

Compound	Formula	M.p. °C.	$[\alpha]_D$	$[\alpha]_{Hg}$	Ref.
Methiodide		270			54
		260			55
Δ^2 - Δ^1 -Solanidene (XV) ^a	$C_{27}H_{41}N$	257-258			6
Δ^2 -Solanidene (XVI)	$C_{27}H_{43}N$	178	+139° (C_6H_6)		45
Δ^2 -Solanidene N-oxide	$C_{27}H_{43}ON$	165	+67.9° ($CHCl_3$)		6, 40
2,3-Oxidosolanidene N-oxide	$C_{27}H_{43}O_2N$	227			57
Solanidan-2,3-diol	$C_{27}H_{45}O_2N$	242-243			57
Δ^4 -Solanidene	$C_{27}H_{43}N$	218-219			57
Δ^5 -Solanidene (XIX)	$C_{27}H_{43}N$	164		+32.4° (C_6H_6)	45
		163			25
		161-162			54
		163			53
Δ^3 -5 β -Solanidene (XVII) (Δ^3 -Allo-solanidene)	$C_{27}H_{43}N$	145.5-146.5	+34.0° ($CHCl_3$)		40
Solanidane (V)	$C_{27}H_{45}N$	165	+30.4° ($CHCl_3$)		55
		164			6
		161.5-162.5	+33.1° ($CHCl_3$)		40
		285			55
Methiodide					
5 β -Solanidane (XVIII) (Allo-solanidane)		140-142			
7-Oxosolanidine acetate (XX) ^b	$C_{29}H_{43}O_3N$	235.5	+34.8° ($CHCl_3$)		40
Dibenzoyl- Δ^5 -solaniden-3 β ,7-diol (XXI)					48
Δ^5 ,7-Solanidien-3 β -ol (XXII) ^c	$C_{41}H_{51}O_4N$	214.5	+112°		48
Benzoyl- Δ^6 ,7-solanidien-3 β -ol	$C_{27}H_{41}ON(+1H_2O)$	180			48
"Trichlorsolanidane"	$C_{34}H_{45}O_2N$	190	-48°		48
	$C_{27}H_{40}NCl_3$	188-190, 270			54

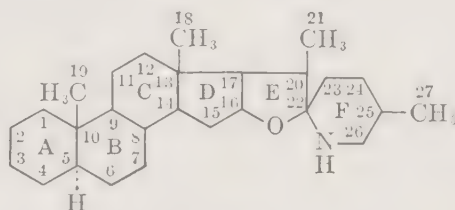
^a Digitonin precipitable.^b λ_{max} . 237 m μ (log ϵ 4.2) (45).^c λ_{max} . 240 m μ (log ϵ 4.2) (40).^d Rosenheim-reaction positive.^e λ_{max} . 275 m μ (log ϵ 1.65) (45).^f λ_{max} . 228 m μ (log ϵ 4.38) 234 m μ (log ϵ 4.39) (45).^g λ_{max} . 265 m μ , 275 m μ (log ϵ 3.86).^h λ_{max} . 234 m μ (log ϵ 4.08).ⁱ Rosenheim-reaction positive.^j UV-absorption spectrum identical with that of ergosterol.

solasodine is quite distinct from solasodan-3 β -ol. Its basicity, pK_B 4.36 (11), is the same as that of dihydrosolasodan-3 β -ol, into which it is readily convertible by hydrogenation. It reacts like the former to yield an *O,O',N*-triacetyl and an *N*-nitroso derivative (16).

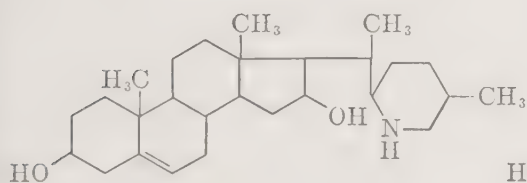
$\Delta^{3,5}$ -Solasodiene, $C_{27}H_{41}ON$, on hydrogenation in ethanol generates two compounds, $C_{27}H_{45}ON$, which are known as " α "- and " β "-solasodane. With platinum oxide in acetic acid on the other hand the diene absorbs three moles of hydrogen to form $C_{27}H_{47}ON$, in which the oxide ring is cleaved as well, to form a dihydrosolasodane (17, 43, 46).



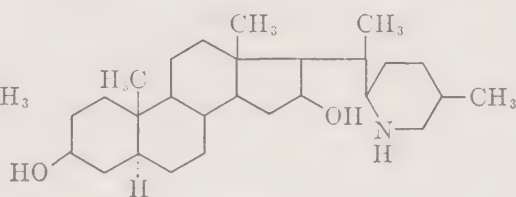
XXX



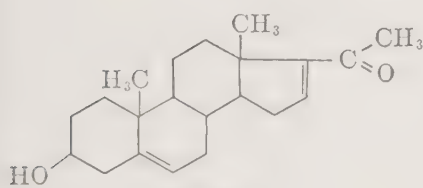
XXXI



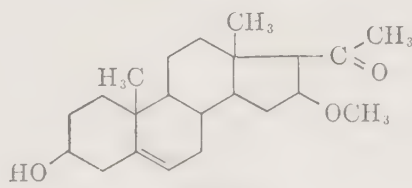
XXXIII



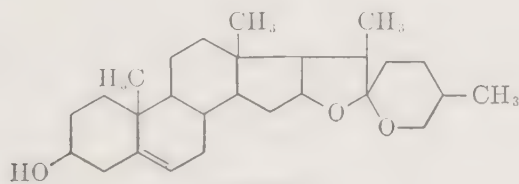
XXXII



XXXIV



XXXV



XXXVI

DEHYDROGENATION. The selenium dehydrogenation of solasodine yielded γ -methylecyclopentenophenanthrene (XXIII), indicating that the skeletal structure is the same as that of the sterols (42).

TRANSFORMATION TO STEROID DERIVATIVES. The conversion of solasodine to sterol derivatives was accomplished in two ways. The oxidation of acetylsolasodine with chromic acid in acetic acid resulted in a

TABLE 4
PROPERTIES OF SOLASODINE AND ITS DERIVATIVES

Compound	Formula	M.p. °C.	$[\alpha]_D$	Ref.
Solasodine (XXX) ^a	$C_{27}H_{43}O_3N$	199	-92.4° (C_6H_6)	46
Hydrochloride ^b		197.5-198.5	-97.1°, -80.4° (CH_3OH)	4, 17
		314	-68.0° (CH_3OH)	4
Hydrobromide		314.5-315		5
		302		17
		299		
Hydriodide		293		5
		291		4
		288		17
Perchlorate				5
Sulfate		262-264		17
Nitrate		293		
Oxalate		269		5
		249		5
		245-246		4
Tartrate		222		5
		220		4
Picrate		144		5
Picolonate		234		4, 5
		232		4
Acetylolasodine	$C_{29}H_{45}O_3N$	193-194		5
		195		46
Benzoylasodine		191-193		17
O-Nitrobenzoylasodine	$C_{34}H_{47}O_3N$	216-217		52
3,5-Dinitrobenzoylasodine		222		46
N-Nitrosolasodine ^c	$C_{27}H_{42}O_3N_2$	191-193		17
		260		17
		260.5-262.5 (dec)		38
				17

Δ^4 -Solasonen-3-one ^d	$C_{27}H_{41}O_2N$	184-185 186	46 17
Δ^4 -Solasonen-3 β -ol ^e	$C_{27}H_{43}O_2N$	170	49
Acetyl- Δ^4 -solasonen-3 β -ol	$C_{29}H_{45}O_3N$	175	49
Δ^4 -Solasonen-3 α -ol ^f	$C_{27}H_{43}O_2N$	220	49
Solasonen-3 β -ol ^g	$C_{27}H_{45}O_2N$	208.5-210.5 209	17 49
Picrate		141.5-142	15
Hydriodide		284	15
Perchlorate		141-142	15
Acetylsolasonen-3 β -ol	$C_{29}H_{47}O_3N$	214	49
N-Nitrosolasonen-3 β -ol	$C_{27}H_{44}O_3N_2$	272	15
$\Delta^{3,5}$ -Solasonine (Solanosodine) ^h	$C_{27}H_{41}ON$	176-177 174-175 169.5-170.5 318	43 46 17 17
Hydrochloride			
" α "-Solasonane	$C_{27}H_{45}ON$	175-176 208	15 15
Picrate			
" β "-Solasonane	$C_{27}H_{45}ON$	132-134 198-200	15 15
Picrate			
Dihydrosolasonen-3 β -ol (XXXII) ⁱ	$C_{27}H_{47}O_2N$	286.5-288 285-291, 292-296.5 288-291	46 17 16

^a 2 active hydrogens (46); color reactions (5, 46); crystallography (5); digitonin precipitable (42); the salts of solasonine may generally be recrystallized from dilute ethanol and melt with decomposition.

^b Crystallography (4).

^c λ_{max} . 240 m μ (log ϵ 3.7), λ_{max} . 375 m μ (log ϵ 2.0) (15).

^d Opt. inactive (46); λ_{max} . 232 m μ (log ϵ 4.18) (46).

^e Rosenheim-reaction positive; digitonin precipitable.

^f Rosenheim-reaction positive; digitonin nonprecipitable.

^g Digitonin precipitable (49).

^h λ_{max} . 234 m μ (log ϵ 4.34), λ_{max} . 234.5 m μ (log ϵ 4.44), λ_{max} . 240 m μ (log ϵ 4.17); Rosenheim-reaction positive (17).

ⁱ 3 active hydrogens (15); digitonin precipitable (46).

TABLE 4 (Continued)

Compound	Formula	M.p. °C.	$[\alpha]_D$	Ref.
Hydriodide		283		17
Pierate		321-322		15
N'-Methyldihydrosolasodan-3 β -ol Hydriodide	C ₂₈ H ₄₉ O ₂ N	140		15
		275		15
		285-286		15
Diacyldihydrosolasodan-3 β -ol	C ₃₁ H ₅₁ O ₄ N	165		49
O,O',N'-Triacyldihydrosolasodan-3 β -ol	C ₃₃ H ₅₃ O ₅ N	153-154		15
N'-Nitrosodihydrosolasodan-3 β -ol ^j	C ₂₇ H ₄₆ O ₃ N ₂	254-255		15
Dihydro- Δ^5 -solasoden-3 β -ol (XXXIII)	C ₂₇ H ₄₅ O ₂ N	260-264		16
O,O',N'-Triacyldihydro- Δ^5 -solasoden-3 β -ol	C ₃₃ H ₅₁ O ₅ N	169.5-170.5		16
N'-Nitrosodihydro- Δ^5 -solasoden-3 β -ol ^k	C ₂₇ H ₄₄ O ₃ N ₂	250-251		16
Dihydrosolasodane	C ₂₇ H ₄₇ ON	184-186	-18° (CHCl ₃)	15

^j λ_{\max} . 238.2 m μ (log ϵ 3.74), λ_{\max} . 352.5 m μ (log ϵ 1.87).^k λ_{\max} . 238 m μ (log ϵ 3.7), λ_{\max} . 352 m μ (log ϵ 1.8).

Added in proof: R. Kuhn, I. Löw and H. Trischmann, *Angew. Chemie*, **64**, 397 (1952) converted tomatidine into solanidan-3 β -ol. R. Kuhn and I. Löw, *Ber.*, **85**, 416 (1952) degraded tomatidine to tigogenine lactone, proving thus the structure of the rings E and F. It seems, therefore that tomatidine and solanidan-3 β -ol can differ only by configuration about the carbons 16 and/or 22.

mixture which, after hydrolysis with methanolic potash, yielded the acetyl derivatives of $\Delta^{5,16}$ -pregnandien-3 β -ol-20-one (XXXIV) and of 16-methoxy- Δ^5 -pregnen-3 β -ol-20-one (XXXV). The latter was presumably formed from the former by the addition of methanol to the double bond (52).

More important still is the observation that the *N*-nitrososolasodine when digested with dilute acetic acid generates diosgenin (XXXVI), albeit in low yield. The mechanism of this reaction and the structure of the main product of the reaction, which is isomeric with diosgenin, remain to be elucidated (12). Both degradation reactions leading to known steroid derivatives fix the stereochemistry of the carbons on rings A, B, C, and D of solasodine as identical with those in the steroids.

c. Tomatidine. The aglycone which is obtainable by hydrolysis of tomatine, is termed tomatidine, $C_{27}H_{45}O_2N$, and has the same melting point (210–211°) as has the isomeric solasodan-3 β -ol, but is nevertheless different from it. Its chemical reactions so far known indicate that it is a solasodan-3 β -ol, but there are marked differences in the melting points of a number of derivatives. These differences may be due to differences in the structure or the configuration of rings E and F.

Tomatidine has a basic secondary nitrogen, one hydroxyl group, and an oxygen probably in ether linkage. It is saturated and therefore hexacyclic, yields crystalline salts, forms an *N*-nitroso derivative and an *O,N*-diacetyl derivative (26, 33, 51).

In the presence of a platinum oxide catalyst tomatidine absorbs one mole of hydrogen; in this reaction a cyclic ether is split. The same hydrogenolysis can be achieved with lithium aluminum hydride whereby

TABLE 5
PROPERTIES OF TOMATIDINE AND ITS DERIVATIVES

Compound	Formula	M.p. °C.	$[\alpha]_D$	Ref.
Tomatidine (XXXVII) ^a	$C_{27}H_{45}O_2N$	210–211		26
		205–208.5		51
Hydrochloride			$-8.8^\circ \pm 2.1$ (CH ₃ OH)	18
<i>O,N</i> -Diacetyltomatidine ^b	$C_{31}H_{49}O_4N$	193–194		26, 33, 51
<i>N</i> -Nitrosotomatidine ^c	$C_{27}H_{44}O_3N_2$	194–195		51
Dihydrotomatidine (XXXVIII)	$C_{27}H_{47}O_2N$	194–195		26
<i>O,O',N</i> -Triacetyldihydrotomatidine	$C_{33}H_{53}O_5N$			26
<i>O,O',N</i> -Triacetylisotomatidine (XXXIX) (Compound A)	$C_{33}H_{51}O_5N$	105–107	-11.6° (CHCl ₃)	51
<i>N</i> -Acetylisotomatidine	$C_{29}H_{47}O_3N$	210–215		51
Dihydro- <i>O,O',N</i> -triacetyliso-tomatidine	$C_{33}H_{53}O_5N$	119–122		51

^a Digitonin precipitable; IR-absorption spectrum (26).

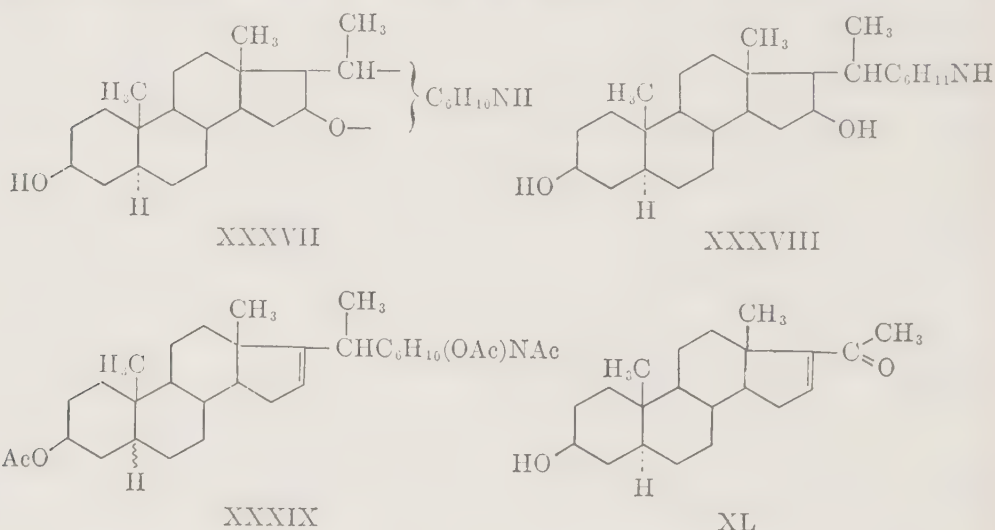
^b IR-absorption spectrum (26).

^c λ_{max} , 233 m μ (log ϵ 3.87), λ_{max} , 360 m μ (log ϵ 1.83).

a dihydrotomatidine, $C_{27}H_{47}O_2N$ (XXXVIII), is formed. This is different from the isomeric dihydrosolasodan- 3β -ol, but like this it gives rise to a neutral O,O',N -triacyl derivative, $C_{33}H_{53}O_5N$ (26, 33, 51).

Energetic treatment of tomatidine with acetic anhydride generates an unsaturated O,O',N -triacyl derivative, $C_{33}H_{51}O_5N$ (XXXIX), which may be reduced to a dihydro derivative that is isomeric, but not identical, with that obtainable from the lithium aluminum hydride reduction product (XXXVIII).

The unsaturated triacyl derivative (XXXIX) on oxidation with chromic acid in acetic acid and subsequent hydrolysis yields Δ^{16} -allo-pregnen- 3β -ol-20-one (XL) (51). There remains still to be determined the structures and configurations of rings E and F. See addendum, p. 266.



d. Solanocapsine. Solanocapsine was isolated from the leaves of *S. pseudocapsicum* L. (2, 7). It is evidently present in the free form since attempts to isolate an alkaloid glycoside under mild conditions were unsuccessful (53). The early empirical formula, $C_{26}H_{44}O_2N_2$ (2), is untenable in view of the results of E. Schlittler (53) which indicate $C_{27}H_{46}O_2N_2$, a formula with the same number of carbon atoms as the other *Solanum* alkalamines. Like the other alkalamines of this group selenium dehydrogenation affords γ -methylcyclopentenophenanthrene and 2-ethyl-5-methylpyridine (2, 53).

One of the nitrogens is primary and the other secondary, and both are basic. In confirmation of this fact, solanocapsine yields an N,N,N' -trimethyl derivative, $C_{30}H_{52}O_2N_2$, on reaction with formaldehyde and formic acid (53). The nature of the oxygen functions are little understood, but they may be present as nonreactive hydroxyl (tertiary) and as ether linkage. The action of acetic anhydride yields a neutral N,N' -diacyl

derivative only (2). Solanocapsine is not reducible either with palladium catalyst in methanol or with platinum oxide catalyst in acetic acid, and since it therefore appears to be saturated it is hexacyclic (2, 50).

The action of methanolic potassium hydroxide on solanocapsine serves to eliminate one molecule of water with the formation of apo-solanocapsine, $C_{27}H_{42}ON_2$. This and solanocapsine react with nitrous acid to yield the same *N*-nitroso compound ($C_{27}H_{42}O_3N_2$?) in which the original hydroxyl has been eliminated as water with the formation of a double bond, and in which the primary amino group has been replaced by a hydroxyl, the secondary nitrogen forming the nitroso compound, which can be catalytically reduced in the presence of palladium to saturate the double bond. Oxidation of the nitroso compound yields a neutral and an acidic product whose formulas are uncertain (2). With acetone solanocapsine yields a condensation product (2).

It may therefore be concluded that solanocapsine has the skeletal structure common to steroids, and a relation to solasodine is possible. The positions of one of the nitrogens and of both oxygens remain in doubt.

TABLE 6
PROPERTIES OF SOLANOCAPSINE AND ITS DERIVATIVES

Compound	Formula	M.p. °C.	$[\alpha]_D$	Ref.
Solanocapsine	$C_{27}H_{46}O_2N_2$	222	+25.5°	2
Dihydrochloride		280		2
Aposolanocapsine	$C_{27}H_{44}ON_2$ (?)	amorph.		2
<i>N</i> -Nitroso compound ^a	$C_{27}H_{42}O_3N_2$	194		2
Dihydro- <i>N</i> -nitroso compound	$C_{27}H_{44}O_3N_2$	211–212		2
<i>N,N'</i> -Diacetylsolanocapsine		amorph. 150–160		2
Condensation product of solanocapsine with acetone		233		2

^a 2 active hydrogens.

The presence of a second and amorphous alkaloid of the formula $C_{26}H_{42}O_4N_2$ in the leaves of *S. pseudocapsicum* has not been confirmed. A preparation from the mother liquors of solanocapsine was subjected to selenium dehydration and gave rise to γ -methylcyclopentenophenanthrene and a mixture of pyridine bases. From the latter the picrates of 2-methyl-5-ethylpyridine, m.p. 162°, and of 4-methyl-2-ethylpyridine, m.p. 125°, were isolated (2). These observations are difficult to interpret in view of our present knowledge of the structure of the *Solanum* alkalamines and require experimental confirmation.

e. Less-known Alkalamines. The aglycone *solauricidine*, $C_{27}H_{43}O_2N$, from the glycoalkaloid *solauricine*, is isomeric with and very similar to sol-

asodine. The greatest difference between the two is in the melting point of the free bases, that of solauricidine, which is not altered by sublimation (219°), being nearly 20° higher than that of solasodine. Nevertheless there is no observable melting point depression when the two are mixed. Solauricidine like solasodine is dimorphic, and the two respective forms are not distinguishable crystallographically. Their optical rotations are only slightly different, and the salts and other derivatives show only slight differences in melting points and on admixture show no melting point depressions; however, these melting points are almost invariably decomposition points as well (1, 5).

In spite of this correspondence, Bell, Briggs, and Carroll are inclined to the view that the two alkamines are in fact distinct, since it was not possible to convert the one into the other. Furthermore, they succeeded in isolating and separating both alkamines from *S. auriculatum* by fractional crystallization and the differences persisted after sublimation (5).

A similar alkamine, $C_{27}H_{43}O_2N$, probably isomeric with solasodine, was obtained by hydrolysis of glycoalkaloid from *S. panduraeforme* (60).

The alkamine *solanugustidine*, $C_{27}H_{43}O_2N$, is the aglycone of solanugustine, and has not been obtained in crystalline form although a number of crystalline salts and a crystalline acetyl derivative are known. Its properties indicate that it is not identical with either solasodine or with solauricidine (58). Hydrochloride, $C_{27}H_{43}O_2N \cdot HCl$, m.p. 325° ; hydrobromide, $C_{27}H_{43}O_2N \cdot HBr$, m.p. 320° (dec.) nitrate, $C_{27}H_{43}O_2N \cdot HNO_3$, m.p. 290° ; sulfate, $B_2 \cdot H_2SO_4$, m.p. above 330° ; acetylsolanugustidine, $C_{29}H_{45}O_3N$, m.p. 256° (58).

III. Veratrum Alkaloids

These glyco- and ester-alkaloids which have been isolated from *Veratrum* and related genera and which have been adequately characterized as single pure substances are given in Table 7 together with their alkamine and sugar components.*

In addition to the conjugated bases the free alkamines, rubijervine, $C_{27}H_{43}O_2N$, isorubijervine, $C_{27}H_{43}O_2N$, veratramine, $C_{27}H_{39}O_2N$, jervine, $C_{27}H_{49}O_3N$, and zygadenine, $C_{27}H_{43}O_7N$, were isolated directly. It is not certain that these alkamines are primary plant products. They may be the products of enzymatic or chemical hydrolysis occasioned during isolation. Other alkaloids in this series have been described, but they have either been inadequately characterized or have proved to be mixtures, e.g., cevadilline, sabadine, and two unnamed alkaloids described by Bredemann, Jacobs, and Craig. It should be noted that the earlier work

* In the meantime were isolated from *Veratrum* and *Zygadenus* species, 8 new steroid alkaloids; these could not be included in Table 7 (44a, 44b, 45, 49a, 60b).

TABLE 7

Glycoalkaloid	Alkamine	Sugar
Veratrosine $C_{33}H_{49}O_7N$	Veratramine $C_{27}H_{39}O_2N$	D-Glucose
Pseudojervine $C_{33}H_{49}O_8N$	Isojervine $C_{27}H_{39}O_3N$	D-Glucose
Ester-alkaloid	Alkamine	Acid
Cevadine $C_{32}H_{49}O_9N$	Cevagenine or Cevine $C_{27}H_{43}O_8N$	Angelie
Veratridine $C_{36}H_{51}O_{11}N$	Cevagenine or Cevine $C_{27}H_{43}O_8N$	Veratric
Protoveratridine $C_{31}H_{49}O_9N$	Germine $C_{27}H_{43}O_8N$	D-(-)- α -Methylbutyric
Germerine $C_{37}H_{59}O_{11}N$	Germine $C_{27}H_{43}O_8N$	D-(-)- α -Methylbutyric (+)- α -Oxy- α -methylbutyric
Germidine $C_{34}H_{53}O_{10}N$	Germine $C_{27}H_{43}O_8N$	Acetic, D-(-)- α -Methylbutyric
Neogermitrine (Alkaloid A) $C_{36}H_{55}O_{11}N$	Germine $C_{27}H_{43}O_8N$	2 Moles Acetic, D-(-)- α -Methylbutyric
Germitrine $C_{39}H_{61}O_{12}N$	Germine $C_{27}H_{43}O_8N$	Acetic, D-(-)- α -Methylbutyric, (+)- α -Oxy- α -methylbutyric
Protoveratrine $C_{39}H_{51}O_{13}N$	Protoverine $C_{27}H_{43}O_9N$	Acetic, D-(-)- α -Methylbutyric, (+)- α -Oxy- α -methylbutyric
Veratrolyzygadenine $C_{36}H_{51}O_{10}N$	Zygadenine $C_{27}H_{43}O_7N$	Veratric
Vanilloylzygadenine $C_{35}H_{49}O_{10}N$	Zygadenine $C_{27}H_{43}O_7N$	Vanillic
Escholerine $C_{41}H_{63}O_{13}N$	Protoverine $C_{27}H_{43}O_9N$	Acetic, α -Methylbutyric

on the isolation of the alkaloids of various *Veratrum* and *Sabadilla* species was not carried out with the care that later work has shown to be necessary. In many cases therefore more careful work, particularly under conditions that will avoid hydrolysis, is desirable.

1. GLYCOSIDES

a. *Veratrosine*.

OCCURRENCE AND ISOLATION. Jacobs and Craig (36) isolated veratramine from the roots and rhizomes of *Veratrum viride* Ait. The powdered drug was first moistened with ammonia and then extracted with benzene. The residue was then extracted a number of times at

room temperature with ethanol containing a small amount of ammonia. The extract was worked up in the usual manner to yield a mixture of veratrosine and pseudojervine, from which the latter was separated by fractional crystallization from ethanol, in which it is only sparingly soluble. The veratrosine was separated from the mother liquors and purified by recrystallization from methanol-water (3:1) and then from methanol.

PROPERTIES. Veratrosine, $C_{33}H_{49}O_7N$, melts with decomposition at $242-243^\circ$, the exact temperature depending somewhat on the rate of heating; $[\alpha]_D + 53^\circ$ (ethanol-chloroform, 1:1). Hydrolysis with 2% aqueous hydrochloric acid yields D-glucose and the aglycone veratramine, $C_{27}H_{39}O_2N$ (36).

b. *Pseudojervine*.

OCCURRENCE AND ISOLATION. The glycoside pseudojervine was first isolated by Wright and Luff (69) from the rhizomes of *V. album* L. where it is accompanied by veratrosine. The impure pseudojervine, whose isolation is described above, may be purified by recrystallization from dilute methanol (36, 52, 53).

PROPERTIES. Pseudojervine, $C_{33}H_{49}O_8N$, is reported to melt at 299° , $300-307^\circ$, $300-301^\circ$ and 305° , with decomposition, the exact temperature depending on the rate of heating and on the solvent chosen for crystallization; $[\alpha]_D - 139^\circ$ (ethanol-chloroform, 7 + 43), -133° (ethanol-chloroform, 1:3); color reaction with sulfuric acid, green. Five active hydrogens are shown by a Zerewitinoff determination. Hydrochloride, m.p. $254-256^\circ$ (dec.); thiocyanate, m.p. $245-246^\circ$ (dec.); the picrate and the aurichloride are amorphous; N-nitroso derivative, $C_{33}H_{48}O_9N_2$, white flakes from ethanol, m.p. 261° (dec.) (36, 52, 53, 69). Hydrolysis with 2% aqueous hydrochloric acid yields D-glucose and isojervine, $C_{27}H_{39}O_3N$ (36).

2. ESTERS

a. *Cevadine*.

OCCURRENCE. Cevadine, $C_{32}H_{49}O_9N$, which has also been described under the names veratrine and crystalline veratrine, was early recognized as the most abundant alkaloid of *Sabadilla* seeds, *Veratrum sabadilla* Retz. (*Schoenocaulon officinale* A. Gray). It was described by Merck (48) and further characterized by Schmidt and Köppen (59) and by Blount (3).

ISOLATION. The powdered seeds are repeatedly extracted with hot water acidified with sulfuric or hydrochloric acid. The combined extract is evaporated to a weight equal to that of the seeds taken, allowed to settle, filtered, and precipitated with ammonia. The brown resinous precipitate is extracted repeatedly with boiling water until the extract is

colorless. The dried residue is exhaustively extracted with ether, and the residue from the extract dissolved in dilute hydrochloric acid and precipitated with ammonia. Solution and precipitation are repeated and the precipitate, dried at 40°, may then be crystallized from ethanol to yield cevadine (48, 60).

PROPERTIES AND DERIVATIVES. Cevadine, $C_{32}H_{49}O_9N$, m.p. 205° (from ethanol and dried at 140°); $[\alpha]_D + 12.5^\circ$ (ethanol), $+6.38^\circ$ (pyridine), $+1.25^\circ$ (acetone) (18, 46, 59); perchlorate, m.p. 256–258° (60a); the hydrochloride and the acid sulfate are amorphous; aurichloride, m.p. 182° (dec.); mercurichloride, m.p. 172° (dec.); picrate, becomes black at 225° without melting; methiodide, 220–230° (dec.), yields the quaternary base on treatment with silver oxide, which then forms an aurichloride melting at 149° (1, 3, 15, 18).

Benzoylcevadine benzoate, $C_{39}H_{53}O_{10}N \cdot C_7H_6O_2 \cdot H_2O$ (retains one mole of water after drying at 120°); benzoylcevadine, m.p. 257° (precipitated from ethanol-acetic acid with ammonia); benzoylcevadine hydrochloride (retains one mole water when heated to 130°); benzoylcevadine hydriodide, m.p. 220–222°; benzoylcevadine nitrate, m.p. 194–195°; acetylcevadine, m.p. 182°, resolidifies and then melts again at 234° (amorphous); *o*-nitrobenzoylcevadine, m.p. 236° (dec.) (precipitated from a tartaric acid solution with sodium hydroxide), $[\alpha]_D - 37.5^\circ$ (ethanol) (17, 46); dihydrocevadine I, $C_{32}H_{51}O_9N$, m.p. 222–223°, $[\alpha]_D - 0.69^\circ$ (ethanol) (60a); dihydrocevadine II, $C_{32}H_{51}O_9N$, m.p. 181–184°, solidifies and remelts at 190–192°, $[\alpha]_D + 7.09^\circ$ (ethanol) (60a).

Mild alkaline hydrolysis converts cevadine into the alkamine cevagenine, $C_{27}H_{43}O_8N$, and angelic acid. Prolonged treatment with alkali yields cevine and a mixture of tiglic and angelic acid. Finally, alcoholysis with methanolic hydrogen chloride yields methyl tiglate. It is therefore probable that cevadine is the angelic ester of cevagenine and that cevine and tiglic acid are secondary products. Catalytic hydrogenation of cevadine in acetic acid with palladium gives rise to dihydrocevadine I and II, which on hydrolysis yield D-(–)- and L-(+)- α -methylbutyric acids, respectively. Evidently only the double bond in the angelic acid moiety is reduced (1, 16, 25, 60a, 68).

Cevadine shows the presence of four (?) active hydrogens (Zerewitinoff); on dry distillation it yields tiglic acid and β -picoline, which was identified by its chloroplatinate, m.p. 196–197° (dec.). It was possible to isolate β -pipecoline from the products of its distillation with lime (1, 18).

b. Veratridine.

OCCURRENCE AND ISOLATION. Veratridine, $C_{36}H_{51}O_{11}N$, occurs along with cevadine in the seeds of *V. sabadilla*. Wright and Luff were the first

to isolate these ester-alkaloids, which were more exactly described by Blount. Veratridine is separable from commercial veratrine as its sparingly soluble amorphous nitrate. This is dissolved in 2*N* sulfuric acid and the solution treated with a saturated solution of ammonium sulfate to incipient turbidity, whereupon the veratridine sulfate slowly crystallizes in slender needles. Purification may also be achieved with the aid of its easily crystallizable perchlorate (3, 60a, 68).

Veratridine is amorphous, and unlike cevadine it is practically insoluble in water; $[\alpha]_D + 8^\circ$ (ethanol); it retains water very tenaciously—drying in a high vacuum at 110° is necessary before satisfactory analytical values for $C_{36}H_{51}O_{11}N$ can be obtained.

Veratridine sulfate is very hygroscopic; the perchlorate when crystallized from water or from ethanol melts at $256\text{--}258^\circ$ (3, 60a).

Mild hydrolysis with alcoholic alkali yields cevagenine and veratric acid, whereas energetic treatment with the same reagent yields the same acid and cevine (3, 60a).

c. Protoveratridine. This alkaloid was first isolated by Salzberger (53) from the rhizomes of *V. album*. Poethke (50, 51) showed that this ester-alkaloid is not present as such in the plant but is formed by partial alkaline hydrolysis of a higher ester-alkaloid. It is sparingly soluble in ethanol and other solvents and is consequently easily separated fractionally with chloroform-ethanol from its congeners (19, 50, 51, 53).

PROPERTIES. Protoveratridine, $C_{31}H_{49}O_9N$, m.p. $266\text{--}267^\circ$ (dec.) (precipitated from ethanol-acetic acid, 3:1, by ammonia), m.p. 265° (chloroform-ethanol), $[\alpha]_D - 14^\circ$ (pyridine, determined by H. L. H. on Poethke's analytical sample); color reactions—with sulfuric acid, violet cherry red; concentrated hydrochloric acid, bright red; hydrochloride, m.p. $243\text{--}245^\circ$ (dec.) (from ethanol by treatment with hydrochloric acid); chloroplatinate, m.p. $195\text{--}200^\circ$ (dec.); aurichloride, amorphous; pierate, m.p. $244\text{--}246^\circ$ (dec.) (ethanol-acetone) (51, 53).

On hydrolysis with methanolic potash protoveratridine yields the alkamine germine, $C_{27}H_{43}O_8N$, and D-(–)- α -methylbutyric acid, $[\alpha]_D - 23.1^\circ$ (water) (51).

d. Germerine.

OCCURRENCE AND ISOLATION. The mixture of bases from *V. album* was fractionated by Poethke (50) into a fraction more soluble in ether from which germerine was obtained. More recently, Fried and co-workers (19) described a simple procedure for isolating the alkaloid from *V. viride* Ait.

The benzene extracts of a crude alkaloid mixture contain the alkamines as well as the ester-alkaloids. The former are largely eliminated by crystallization and the amorphous ester-alkaloid mixture is acetylated and extracted with 5% tartaric acid. The resultant extracts, mostly

tertiary bases, are first partitioned between benzene and 2*M* acetate buffers and finally purified by chromatography through a column of acid alumina (prior treatment with sulfuric acid). There is thus obtainable not only the germerine but six other ester-alkaloids, germidine and germitrine. It is not certain whether germerine occurs as such in the plant or is formed during its isolation, as appears to be the case with germitrine (19).

PROPERTIES AND DERIVATIVES. Germerine, $C_{37}H_{59}O_{11}N$, m.p. 193° (dec.) (benzene), m.p. $203-204^{\circ}$ (methanol); $[\alpha]_D - 8.7^{\circ}$ (pyridine), $+11^{\circ}$ (chloroform); hydrochloride, m.p. 215° (dec.); aurichloride, amorphous, m.p. 153° (dec.); hydrobromide, m.p. $212-213^{\circ}$ (dec.) (water); thiocyanate, m.p. $221-223^{\circ}$ (dec.) (dil. ethanol); $230-231^{\circ}$ (dil. methanol); picrate, m.p. $186-187^{\circ}$ (dec.) (acetone-ether); acid sulfate, crystalline (19, 50, 51).

Alkaline hydrolysis of germerine yields the alkamine germine, D-(-)- α -methylbutyric acid, $[\alpha]_D - 22^{\circ}$, -25° (water), and (+)- α -hydroxy- α -methylbutyric acid, m.p. $72-73^{\circ}$, $[\alpha]_D + 4.4^{\circ}$ (water). With baryta at 40° it yields protoveratridine on partial hydrolysis and ultimately germine (19, 51).

e. Germidine.

OCCURRENCE AND ISOLATION. This alkaloid was first described by Fried and co-workers (19). It was obtained as detailed above from *V. viride*. It is possible that it is formed during the isolation procedure from a higher alkamine ester.

PROPERTIES AND DERIVATIVES. Germidine, $C_{34}H_{53}O_{10}N$, is dimorphic and melts at $198-200^{\circ}$ or $230-231^{\circ}$ (dec.) (dil. ethanol); $[\alpha]_D + 13^{\circ}$ (chloroform), -11° (pyridine); thiocyanate, m.p. $242-244^{\circ}$ (dec.) (dil. methanol). Alkaline hydrolysis of germidine gave rise to germine and a mixture of acetic and D-(-)- α -methylbutyric acid, which were obtained in the form of their *p*-phenylphenacyl esters (19).

f. Germitrine. The isolation and occurrence are described under germerine.

PROPERTIES. Germitrine, $C_{39}H_{61}O_{12}N$, m.p. $216-219^{\circ}$ (dec.) (dil. acetone); $[\alpha]_D - 69^{\circ}$ (pyridine), -4° (chloroform); thiocyanate, m.p. $231-232^{\circ}$ (dec.) (dil. acetone).

Methanolysis of germitrine yields germerine and methyl acetate. Furthermore, germerine is formed from germitrine when the latter is passed through a column of alumina that has been pretreated with acetic acid (19).

g. Protoveratrine.

OCCURRENCE AND ISOLATION. Protoveratrine was first obtained by Salzberger (53) from the rhizomes of *V. album*. This ester-alkaloid may be isolated from plant material by the so-called "metaphosphoric acid"

procedure, but the so-called "baryta" procedure presumably destroys it.

The crude drug is first defatted with ether or hexane extraction and then extracted with 80% ethanol. The residue from the evaporated extract is taken up in dilute acetic acid and the clarified solution treated with solid metaphosphoric acid until the further addition of acid yields no more precipitate. There is thus eliminated a large amount of amorphous material as well as most of the jervine and rubijervine. The filtrate from the above precipitate is strongly basified with ammonia, the amorphous precipitate removed, and the filtrate exhausted with ether. The protoveratrine crystallizes when the ether extract is concentrated to a small volume. The ether mother liquors on appropriate treatment yield small amounts of jervine and rubijervine (53).

Craig and Jacobs (12) have described an isolation procedure in which the plant material is first extracted with benzene and the alkaloids are then extracted with aqueous ammonia.

PROPERTIES AND DERIVATIVES. Protoveratrine, $C_{39}H_{61}O_{13}N$, m.p. 245–250° (dec.) (ethanol); m.p. 273–276° (dec.); $[\alpha]_D - 9.1^\circ$ (chloroform), -40° (pyridine); it dissolves in cold sulfuric acid to yield a colorless solution that becomes intensely violet on heating; hydrochloride, m.p. 234–236° (dec.) (chloroform-ether); aurichloride, m.p. 199° (dec.) (acetone-ether); hydrobromide, m.p. 230–232° (dec.); hydriodide, m.p. 247–248° (dec.) (acetic acid); thiocyanate, m.p. 221–223° (dec.) (methanol); picrate, m.p. 216–220° (dec.) (acetone-ether) (12, 51, 53).

Protoveratrine on alkaline hydrolysis yields the alkamine protoverine, $C_{27}H_{43}O_9N$, acetic acid, D-(–)- α -methylbutyric acid $[\alpha]_D - 24^\circ$ (water) and (+)- α -hydroxy- α -methylbutyric acid. Methanolysis has served to yield methyl (+)- α -hydroxy- α -methylbutyrate (19, 51).

Upon dehydrogenation with selenium protoveratrine has yielded 2,5-dimethylpyridine, 2-ethyl-5-methylpyridine, a base C_8H_9ON whose picrate melted at 114–117° (acetone), and (+)- α -hydroxy- α -methylbutyric acid. There were also obtained a compound $C_{17}H_{16}O$, melting at 168–175°, and a base $C_{25}H_{27}N$ whose picrate melted at 235–245° (acetone). These two substances may prove to be identical with cevanthrol and cevanthridine, respectively (12).

h. Neogermitrine (Alkaloid A). Wintersteiner and Fried have reported the isolation from *V. viride* of neogermitrine (alkaloid A), which melted at 231–232° (dil. acetone); $[\alpha]_D - 84^\circ$ (pyridine); thiocyanate, m.p. 226–228°. Upon hydrolysis it afforded germine, $C_{27}H_{43}O_8N$, two moles of acetic acid, and D-(–)- α -methylbutyric acid (21, 44, 65).

i. Alkaloids from Zygadenus venenosus S. Wats. Kupchan and Deliwala recorded the isolation of an ester-alkaloid, $C_{36}H_{51}O_{10}N$, from

this plant in a preliminary communication. Subsequently, they isolated not only germine and zygadenine, but two ester-alkaloids by a counter-current partition procedure. The first, $C_{36}H_{51}O_{10}N$, m.p. 270–271°, $[\alpha]_D - 27^\circ$ (chloroform), λ max. 262, 293 $m\mu$ ($\log \epsilon$ 4.13, 3.85), was identified as veratroylzygadenine. On alkaline hydrolysis it yielded veratric acid and pseudozygadenine, the latter being also obtainable by the action of alkali on zygadenine.

The second alkaloid, $C_{35}H_{49}O_{10}N$, m.p. 258–259° (dec.), $[\alpha]_D - 27.5^\circ$ (chloroform), λ max. 264, 294 $m\mu$ ($\log \epsilon$ 4.07, 3.83), on alkaline hydrolysis yields vanillic acid and pseudozygadenine and is therefore vanillylzygadenine. It was convertible into veratroylzygadenine by treatment with diazomethane (45).

j. Escholerine. *V. eschscholtzii* A. Gray yielded in addition to neogermitrine a new ester-alkaloid, namely, escholerine, $C_{41}H_{61}O_{13}N$,* m.p. 235° (dec.) (dil. acetone), $[\alpha]_D - 30^\circ$ (pyridine). It was characterized as its picrate, m.p. 259° (dec.) and as its aurichloride, m.p. 191°. Alkaline hydrolysis with 0.1 *N* methanolic potash yielded an amorphous alkamine, acetic acid, and α -methylbutyric acid (44).

Stoll and Seebeck (60b) have reported the isolation of an alkaloid, $C_{37}H_{61}O_{12}N$, m.p. 181–183°, $[\alpha]_D - 11.7^\circ$ (pyridine), $+5.4^\circ$ (chloroform) from *V. album*. For it they have proposed the name veralbidine. A thiocyanate, m.p. 235–236°, and a hydrochloride, m.p. 250–251°, are described, but neither the nature of the alkamine nor that of the sugar or acid or both has been reported.

3. ALKAMINES

a. Rubijervine.

ISOLATION. Rubijervine was first obtained by Wright and Luff from the rhizomes of *V. album* (69). Subsequently, Jacobs and Craig (32) gave a more exact description of its isolation. The benzene-extractable alkaloid mixture first deposited the sparingly soluble protoveratrine and other crystalline bases. The amorphous residue was digested with methanolic sodium hydroxide at 60°. The hydrolyzate on fractional crystallization from chloroform-ethanol yielded rubijervine, isorubijervine, and germine in pure form.

REACTIONS AND STRUCTURAL DETERMINATION. Rubijervine, $C_{27}H_{43}O_2N$, has two secondary hydroxyls, and a basic tertiary nitrogen. Hydrogenation indicates one double bond and therefore rubijervine is hexacyclic.

The carbon skeleton of rubijervine has been unambiguously determined because of its conversion into solanidine. The reactions of rubijervine will be discussed on the basis of formula I of Sato and Jacobs

* The correct formula is $C_{41}H_{63}O_{13}N$ (private communication from H. L. H.).

(57), in which only the position of the hydroxyl on C-12 in ring C is in doubt, and the alkaloid is therefore Δ^5 -3 β , x -dihydroxysolanidene. The reaction products of rubijervine will be named in conformity with the steroid nomenclature, but for the alkaloid itself the trivial name will be used.

The two hydroxyls differ in reactivity. While acetic anhydride yields a diacetyl derivative (II), reaction with benzoyl chloride in pyridine at 100° yields a separable mixture (chromatography) of Δ^5 -3 β -benzoyloxy- x -hydroxysolanidene (III) and the dibenzoyl compound IV (32, 57).

The hydroxyls in dihydrorubijervine also behave slightly differently. There have been prepared a diacetyl derivative (VI), 3 β -benzoyloxy- x -hydroxysolanidane (VII), and a dibenzoyl derivative (VIII) (14, 57).

The hydroxyls also behave differently toward oxidizing agents. On dehydrogenation with copper at 290° or on Oppenauer oxidation with acetone and aluminum *tert*-butoxide the hydroxyl at position 3 is converted to a carbonyl to yield the α,β -unsaturated Δ^4 -3-keto- x -hydroxysolanidene (IX). The latter on reduction with aluminum isopropoxide in isopropanol generates a mixture of Δ^4 -3 β , x -dihydroxy- (X) and Δ^4 -3 α , x -dihydroxysolanidene (XI), which are separable by means of digitonin. Since neither of the diols (X or XI) is identical with rubijervine it is evident that the Δ^5 - double bond, in analogy with similar reactions in the sterols and *Solanum* alkaloids, has migrated to the α,β -position with respect to the carbonyl during or subsequent to its oxidative formation (35, 37). The UV-absorption spectrum of compound IX has not been recorded.

Chromic acid in acetic acid oxidizes Δ^5 -3 β -benzoyloxy- x -hydroxysolanidene (III) to the corresponding x -keto compound (XIII), which on hydrolysis yields Δ^5 -3 β -hydroxy- x -ketosolanidene (XII) in which the double bond is not conjugated with the carbonyl (57). When the semicarbazone of the keto compound XIII is heated with alkali there is formed solanidine (IV, p. 254) which was characterized as such and as its acetyl derivative. It has therefore been shown that rubijervine differs from solanidine only in that it has an extra hydroxyl, which on the basis of its comparative nonreactivity and on the basis of a study of the optical rotation of similarly constituted steroids, has been tentatively assigned to the 12 α -position (57).

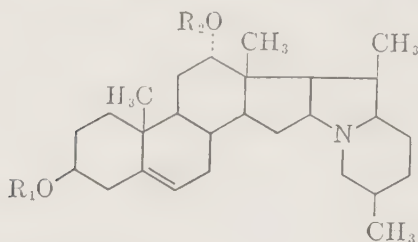
Another route by which rubijervine is convertible into known solanidine derivatives is by way of the saturated diol V, which was first oxidized with chromic acid in acetic acid to the diketone (XIV), the bis(semicarbazone) of which on Wolff-Kischner reduction afforded a mixture of 3 β -solanidanol (IX, p. 256) and solanidane (V, p. 256) (57). Dehydrogenation of rubijervine with selenium gave the typical dehydrogenation

TABLE 8
PROPERTIES OF RUBIJERVINE AND ITS DERIVATIVES

Compound	Formula	M.p. °C.	$[\alpha]_D$	Ref.
Rubijervine (I) ^a	$C_{27}H_{43}O_2N$	240-242	+19.0° (C_2H_5OH)	14
Hydrobromide		265-270		14
Hydriodide		293-296		14
Δ^3 -3 β -Benzoyloxy- <i>r</i> -hydroxysolanidene (III)	$C_{34}H_{47}O_3N$	260-262		57
Δ^3 -3 β - <i>p</i> -Bromo-benzoyloxy- <i>r</i> -hydroxysolanidene	$C_{34}H_{46}O_3NBr$	254-256		52
Δ^3 -3 β - <i>r</i> -Diacetoxysolanidene (II)	$C_{31}H_{47}O_4N$	160-163		32
Δ^3 -3 β - <i>r</i> -Dibenzoyloxy-solanidene (IV)	$C_{41}H_{51}O_4N$	186-187.5		57
3 β - <i>r</i> -Dihydroxysolanidene (V)	$C_{27}H_{45}O_2N$	222		14
3 β - <i>r</i> -Diacetoxysolanidene (VI)	$C_{31}H_{49}O_4N$	216-219		14
3 β -Benzoyloxy- <i>r</i> -hydroxysolanidene (VII)	$C_{34}H_{49}O_3N$	187-190		57
3 β - <i>r</i> -Dibenzoyloxy-solanidene (VIII)	$C_{41}H_{53}O_4N$	266-269		57
Δ^4 - <i>r</i> -Hydroxy-3-ketosolanidene (IX)	$C_{27}H_{41}O_2N$	205-209	+100° (C_2H_5OH)	35, 37
Δ^4 - <i>r</i> -Hydroxy-3-ketosolanidene oxime	$C_{27}H_{42}O_2N_2$	160, solidifies and then melts at 247-254		35
Δ^4 -3 β - <i>r</i> -Dihydroxysolanidene (X) ^b	$C_{27}H_{43}O_2N$	176-178	+46° (C_2H_5OH)	37
Δ^4 -3 α - <i>r</i> -Dihydroxysolanidene (XI) ^c	$C_{27}H_{43}O_2N$	228-231	+63° (C_2H_5OH)	37
Δ^4 -3 β -Benzoyloxy- <i>r</i> -ketosolanidene (XIII)	$C_{34}H_{43}O_3N$	214-216, then solidifies and melts at 233-236		57
Δ^4 -3 β -Hydroxy- <i>r</i> -ketosolanidene (XII) ^d	$C_{27}H_{41}O_2N$	236-238	+45° ($CHCl_3$)	57
Δ^4 -3 β -Benzoyloxy- <i>r</i> -ketosolanidene semicarbazone	$C_{35}H_{48}O_2N_4$	amorph. 265 (dec)		57
3 β -Benzoyloxy- <i>r</i> -ketosolanidene	$C_{34}H_{47}O_3N$	236-241		57
3- <i>r</i> -Diketosolanidene (XIV) ^e	$C_{27}H_{41}O_2N$	215, solidifies and remelts at 242-244	+119° ($CHCl_3$)	57
3- <i>r</i> -Diketosolanidene bis(semicarbazone)	$C_{29}H_{47}O_2N_7$	260-300 (dec)		57

^a Digitonin precipitable; the salts of rubijervine with hydrogen halides are crystallizable from methanol-acetone or methanol-ether.^b Rosenheim-reaction positive; digitonin precipitable.^c Rosenheim-reaction positive; digitonin nonprecipitable.^d UV-absorption spectrum shows a characteristic band for an isolated carbonyl.^e Neither carbonyl is conjugated on the basis of the UV-absorption spectra.

product of the *Solanum* alkaloids, namely, 2-ethyl-5-methylpyridine, together with a hydrocarbon, $C_{18}H_{16}$, m.p. $74-77^\circ$, and a phenol, $C_{15}H_{16}O$, m.p. $136-138^\circ$, the structures of which were not elucidated (32, 57).

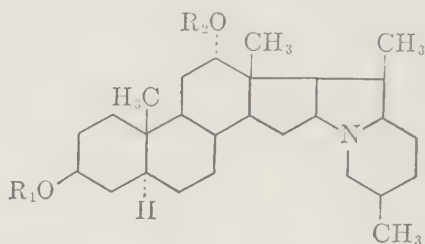


I $R_1 = R_2 = H$

II $R_1 = R_2 = CH_3CO$

III $R_1 = C_6H_5CO$ $R_2 = H$

IV $R_1 = R_2 = C_6H_5CO$

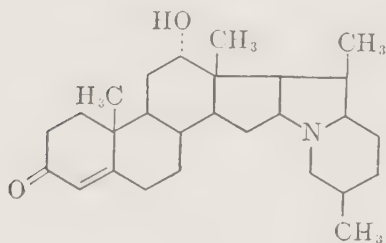


V $R_1 = R_2 = H$

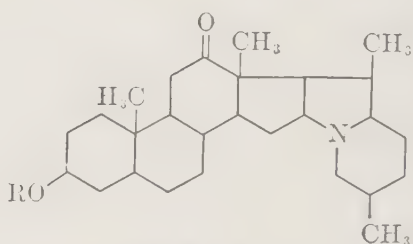
VI $R_1 = R_2 = CH_3CO$

VII $R_1 = C_6H_5CO$ $R_2 = H$

VIII $R_1 = R_2 = C_6H_5CO$

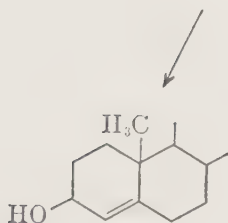


IX

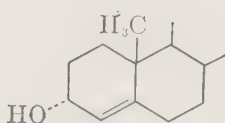


XII $R = H$

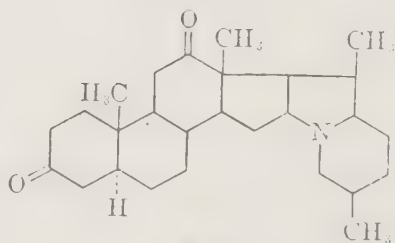
XIII $R = PhCO$



X



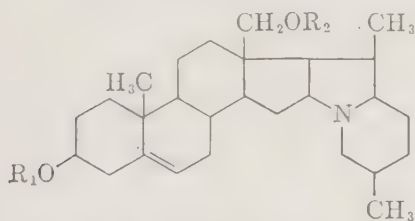
XI



XIV

b. Isorubijervine. Isorubijervine, $C_{27}H_{43}O_2N$, is isomeric with rubijervine and was obtained by Jacobs and Craig from *V. viride* and *V. album* (32). Like rubijervine it has two hydroxyls, but in this case one is secondary and the other primary. It also has a basic tertiary nitrogen and one double bond. Aside from the different location of one of the hydroxyls, the two alkaloids display considerable similarity in their reactions. Although the direct relation of isorubijervine to a *Solanum* alkaloid has not been achieved, there is little doubt that it represents another isomer of hydroxysolanidine. In the following discussion the formula (XV) of Sato and Jacobs (58) will be used. In this formula the primary hydroxyl, which has as yet not been definitely located, is placed on C-18 of the solanidane skeleton. (See addendum on p. 312.)

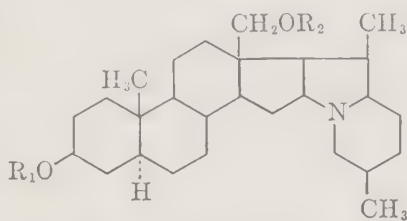
Reaction of isorubijervine with benzoyl chloride in pyridine at 100° forms a mixture of the dibenzoyl derivative (XVII) and a monobenzoyl derivative (XVI) in which the primary hydroxyl is presumably esterified (58). Hydrogenation of the alkaloid with platinum oxide catalyst saturates the double bond to yield dihydroisorubijervine (XVIII), which with acetic anhydride at 100° forms a diacetyl derivative (XIX). The dihydro base yields a monoacetyl derivative (XX) when reacted with acetic anhydride in benzene, the primary hydroxyl only being affected (14, 58).



XV $R_1 = R_2 = H$

XVI $R_1 = H$ $R_2 = PhCO$

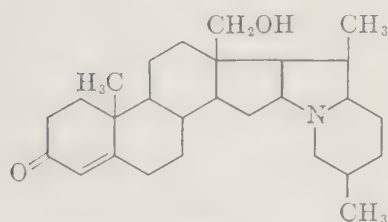
XVII $R_1 = R_2 = PhCO$



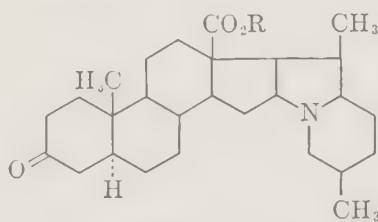
XVIII $R_1 = R_2 = H$

XIX $R_1 = R_2 = CH_3CO$

XX $R_1 = H$ $R_2 = CH_3CO$

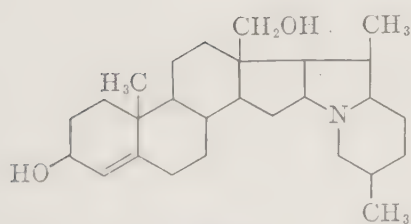


XXI

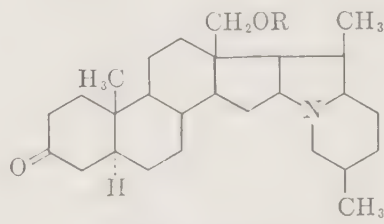


XXIII $R = H$

XXIV $R = CH_3$



XXII



XXV $R = CH_3CO$

XXVI $R = H$

Oppenauer oxidation or heating with copper converts isorubijervine into a monocarbonyl compound in which only the secondary hydroxyl of ring A is affected. The resulting hydroxyketone, $C_{27}H_{41}O_2N$, was characterized as its oxime. Reduction of this compound by the Meerwein-Ponndorf method yields a mixture of epimeric diols from which one, $C_{27}H_{43}O_2N$, is precipitable as its digitonide. The latter gives a positive

reaction with trichloroacetic acid and hence it is regarded as an α,β -unsaturated alcohol. Since it is not identical with isorubijervine it is concluded that the double bond in this alkaloid as well as that in rubijervine and many *Solanum* alkaloids is in the β,γ -position with respect to the secondary hydroxyl (37).

When dihydroisorubijervine is oxidized with chromic acid in acetic-sulfuric acid there is formed a keto carboxylic acid (XXIII) in which the keto group was demonstrated by the formation of an oxime and a semicarbazone, and the carboxyl was demonstrated by the formation of a methyl ester (XXIV), whose reduction with lithium aluminum hydride regenerated dihydroisorubijervine (XVIII) (58).

When isorubijervine is heated with selenium at ca. 340° it yields, like rubijervine and the *Solanum* alkaloids, 2-ethyl-5-methylpyridine. There was also obtained a hydrocarbon, $C_{17}H_{14}$, which was regarded as 1,2-cyclopentenophenanthrene, the formation of which led to the postulate that the primary hydroxyl group is on C-18, since otherwise the formation of γ -methyl-1,2-cyclopentenophenanthrene would be anticipated (37).

c. Veratramine

ISOLATION. Veratramine, $C_{27}H_{39}O_2N$, was first isolated from *V. grandiflorum* O. Loes. (*V. album*, var. *grandiflorum* Maxim.) and later from *V. viride*. It is also obtainable from the glycoalkaloid veratrosine by hydrolysis with 2% hydrochloric acid (36, 56).

It may be conveniently prepared from *V. viride*. The benzene extract of the crude alkaloids when treated with dilute sulfuric acid yields a mixture of the sparingly soluble sulfates of veratramine and jervine. The sulfates are converted to hydrochlorides, conveniently via the free bases. The jervine hydrochloride is only sparingly soluble in ethanol and the veratramine remains in the mother liquor (38).

REACTIONS AND STRUCTURAL DETERMINATION. Tamm and Wintersteiner (61) have proposed the tentative structure XXVII for veratramine, which is related to that of jervine (LVI) and will be used in the following discussion.

It follows from diagnostic reactions that the two oxygens are present as secondary hydroxyls, that the strongly basic nitrogen is secondary, that there is one double bond, and that an aromatic ring is present. Veratramine therefore is pentacyclic in contradistinction to the many other *Solanum* and *Veratrum* alkalamines that have been examined and found to be hexacyclic.

Veratramine is readily acylated to *O,O',N*-triacyl derivatives, acetic anhydride yielding the triacetyl compound XXVIII and benzoyl chloride-pyridine the corresponding tribenzoyl derivative. Alkaline hydrolysis

TABLE 9
PROPERTIES OF ISORUBIJERVINE AND ITS DERIVATIVES

Compound	Formula	M.p. °C.	$[\alpha]_D$	Ref.
Isorubijervine (XV) ^a	$C_{27}H_{43}O_2N$	235-237	+6.5° (C_2H_5OH)	32, 37
Hydrobromide		290-295		32, 37
Benzoyloxyisorubijervine (XVI)	$C_{34}H_{47}O_3N$	188-190		58
Dibenzoyloxyisorubijervine (XVII)	$C_{41}H_{51}O_4N$	220-223		58
"Isorubijervone" (XXI)	$C_{27}H_{41}O_2N$	250-255	+111° (C_5H_5N)	37
Oxime	$C_{27}H_{42}O_2N_2$	250-254		37
"Alloisorubijervine" (XXII) ^b	$C_{27}H_{43}O_2N$	250-251	+63° ($CHCl_3$)	37
Dihydroisorubijervine (XVIII)	$C_{27}H_{45}O_2N$	244		14
Dihydroisorubijervine monoacetate (XX)	$C_{29}H_{47}O_3N$	179-182, 100-103, solidifies and then melts not sharply at 169-180		58 58
Dihydroisorubijervine diacetate (XIX)	$C_{31}H_{49}O_4N$	161-164		58
Keto acetate (XXV) ^c	$C_{29}H_{45}O_3N$	174-177		58
Keto alcohol (XXVI) ^d	$C_{27}H_{43}O_2N$	217-222		58
Keto acid (XXIII) ^e	$C_{27}H_{41}O_3N$	286-288 (dec)	+49° (C_2H_5OH)	58
Oxime	$C_{27}H_{43}O_2N_2$	above 360		58
Semicarbazone	$C_{28}H_{44}O_3N_4$	amorph.		58
Methyl ester ^f	$C_{28}H_{43}O_3N$	162-167	+77° ($CHCl_3$)	58

^a Yields a sparingly soluble digitonide.

^b Digitonin precipitable; Rosenheim-reaction positive.

^c Yields a sparingly soluble 2,4-dinitrophenylhydrazone; λ_{max} , 280 $m\mu$ ($\log \epsilon$ 1.44) (C_2H_5OH); obtained by oxidation of dihydroisorubijervine monoacetate with chromic acid (VI).

^d From the keto-acetate $C_{29}H_{45}O_3N$.

^e By oxidation of dihydroisorubijervine with chromic acid.

^f Not hydrolyzed by ca. 0.3*N* aqueous methanolic sodium hydride at the boiling point.

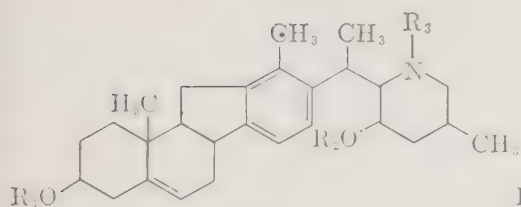
of triacetylveratramine removes the *O*-acetyl groups generating *N*-acetylveratramine (XXIX) (38, 42, 56).

Dihydroveratramine (XXX), readily obtainable from veratramine by catalytic reduction in acetic acid with platinum oxide, also forms a triacetyl derivative (XXXI) which on alkaline hydrolysis yields *N*-acetyldihydroveratramine (XXXII) (38, 56, 61).

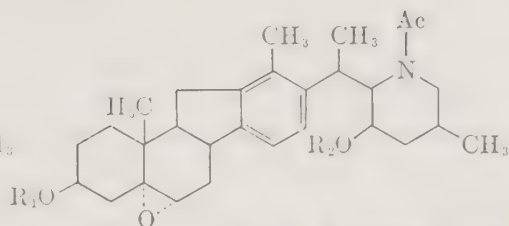
The action of nitrous acid on veratramine yields *N*-nitrosoveratramine and with methyl iodide in the presence of sodium carbonate a quaternary *N*-methyl methiodide is formed which is convertible into the chloride (56, 61). Reaction at the double bond in triacetylveratramine (XXVIII) with osmium tetroxide affords a diol which was isolated as the *O,O',O'',N*-tetracetyl compound, $C_{35}H_{49}O_8N$ (XXXIII). One of the hydroxyls in this compound could not be acetylated and it is therefore probably tertiary (61). Perbenzoic acid reacts with the triacetyl base to form a mixture of two isomeric epoxides, $C_{33}H_{45}O_6N$ (XXXIV and XXXV). The α -isomer, regarded as XXXIV, on hydrolysis with 5% methanolic potash formed the corresponding *N*-acetyl epoxide, $C_{29}H_{41}O_4N$ (XXXVI), and when reacted with dilute sulfuric acid in dilute acetone the epoxide ring was opened with the formation of a dihydroxy-*O,O',N*-triacetyldihydroveratramine (XXXVII) which could be acetylated to a tetracetyl compound (XXXVIII), and which in turn could be dehydrated with thionyl chloride and pyridine to the unsaturated *O,O',O'',N*-tetracetyl compound, $C_{35}H_{47}O_7N$, (XXXIX). The tetracetyl compound XXXVIII is isomeric but not identical with that (XXXIII) obtained from the osmium tetroxide oxidation product.

When the epoxide (presumably the α -form, XXXIV) is reduced with lithium aluminum hydride in ether-benzene and the reaction product reacylated with acetic anhydride-pyridine, there is formed an *O,O'*-diacetyl-*N*-ethylhydroxydihydroveratramine (XL), which readily loses water in contact with thionyl chloride-pyridine to generate an *O,O'*-diacetyl-*N*-ethylveratramine (XLI). During this reduction there is also formed a product which on reacylation proved to be *O,O'*-diacetyl-*N*-ethyldihydroxydihydroveratramine (XLII). Its structure is uncertain but it appears to be formed by hydrolytic rather than reductive cleavage of the epoxide ring (42).

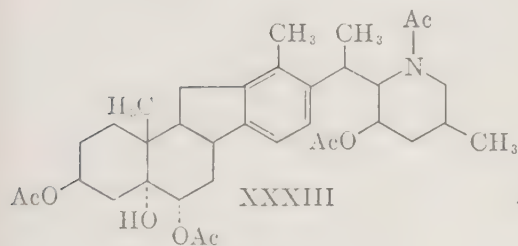
The following observations indicate the position of the double bond and of one of the secondary hydroxyls: Oppenauer oxidation of veratramine affects only one of the hydroxyls to yield an α,β -unsaturated ketone, $C_{27}H_{37}O_2N$, (XLIII) which was isolated as its crystalline hydrochloride. *N*-Acetylveratramine (XXIX) similarly yields the analogous *N*-acetyl derivative, $C_{29}H_{39}O_3N$. Reduction of the unsaturated ketone (XLIII) serves to form a mixture of epimeric alcohols, $C_{27}H_{39}O_2N$ (XLIV



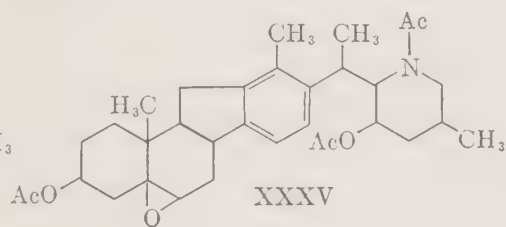
XXVII $R_1 = R_2 = R_3 = H$
 XXVIII $R_1 = R_2 = R_3 = CH_3CO$
 XXIX $R_1 = R_2 = H$ $R_3 = CH_3CO$



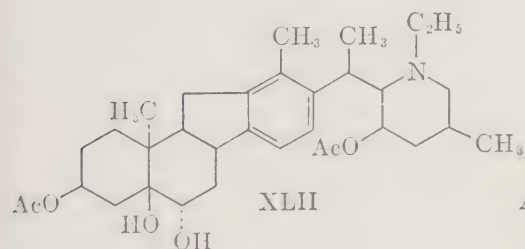
XXXIV $R_1 = R_2 = CH_3CO$
 XXXVI $R_1 = R_2 = H$



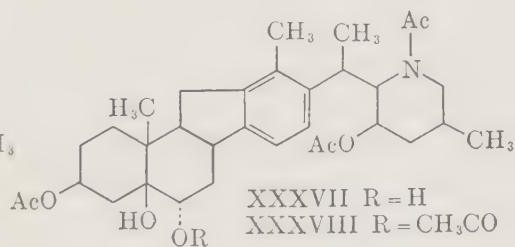
XXXIII



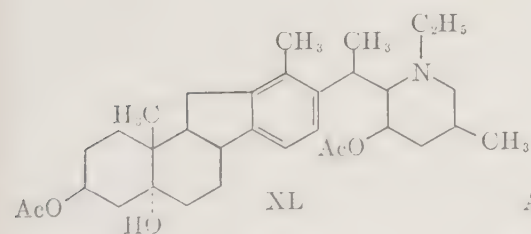
XXXV



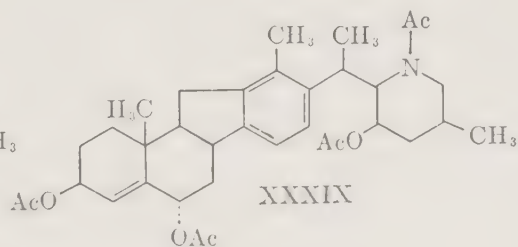
XLII



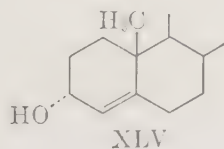
XXXVII $R = H$
 XXXVIII $R = CH_3CO$



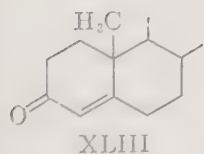
XL



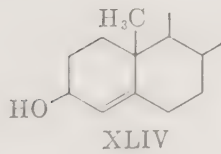
XXXIX



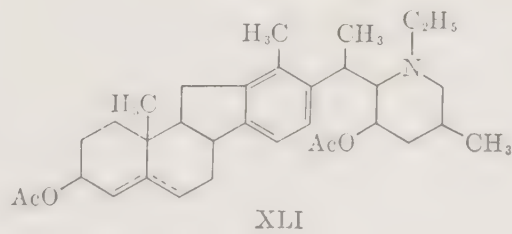
XLV



XLIII



XLIV



LXI

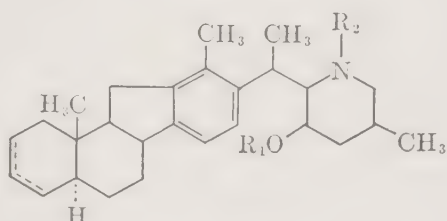
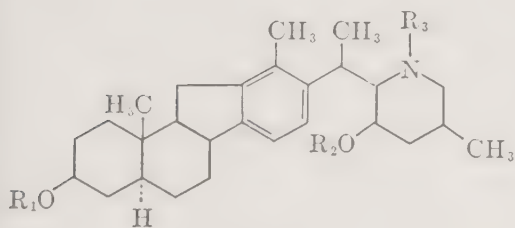
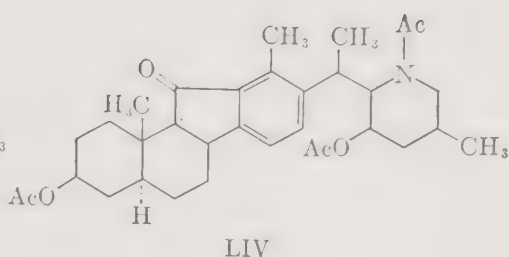
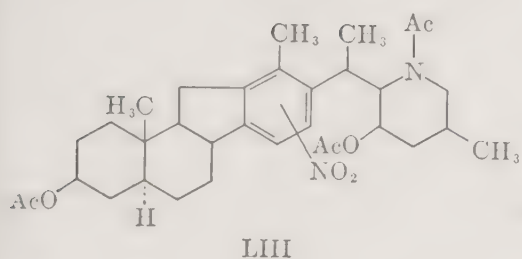
and XLV), which in contradistinction to veratramine give a positive color reaction with trichloroacetic acid. These observations lead to the conclusion, as in many examples already cited, that there is present a β,γ -unsaturated hydroxyl in veratramine (42, 61).

The sluggish reactivity of the second hydroxyl in veratramine is further indicated by the following reactions. Oxidation of dihydroveratramine with chromic acid yields, depending upon the experimental conditions, either the hydroxy ketone, $C_{27}H_{39}O_2N$, or the diketone, $C_{27}H_{37}O_2N$. Similarly, *N*-acetyldihydroveratramine (XXXII) yields either an *N*-acetyl hydroxy ketone, $C_{29}H_{41}O_3N$, or the corresponding diketone, $C_{29}H_{39}O_3N$. The latter is also obtainable from XXXII by Oppenauer oxidation (42, 61). It is therefore evident that the hydroxyl in veratramine which is β,γ - to the double bond is also more reactive in the dihydro base. Consequently, *N*-acetyldihydroveratramine (XXXII) reacts with tosyl chloride in pyridine to yield a monotosylate (XLVI), which with acetic anhydride-pyridine at room temperature is converted into an *O,N*-diacetyl derivative, while acetic anhydride at the boiling point eliminates the tosyl group to form the unsaturated diacetyl compound XLVII. The latter can be hydrolyzed to the *N*-acetyl derivative XLVIII with 2*N* potash, and it can be reduced catalytically in dioxane with palladium-charcoal to dihydro derivative, $C_{31}H_{45}O_3N$ (XLIX) (61).

When *N*-acetyldihydroveratramine (XXXII) is treated with phosphorus oxychloride in pyridine one of the hydroxyls is replaced with chlorine and the other is eliminated with the formation of a double bond to form the compound $C_{29}H_{40}ONCl$ (L). The unsaturated nature of this compound is indicated not only by the fact that it can be oxidized to an α -glycol, isolated as its diacetate, $C_{33}H_{46}O_5NCl$ (LII), with osmium tetroxide, but also by the fact that it can be catalytically reduced to the dihydro compound, $C_{29}H_{42}ONCl$ (LI), without loss of halogen (61).

The presence of the benzene ring in veratramine and many derivatives, indicated by their UV-spectra, can also be demonstrated by chemical means. A mononitro derivative, $C_{33}H_{46}O_7N_2$ (LIII), is obtained when *O,O',N*-triacetyldihydroveratramine (XXXI) is reacted with fuming nitric acid in acetic anhydride-acetic acid. Catalytic reduction of the nitro compound yields an amorphous amine which upon diazotization and coupling with β -naphthol afforded a deep red azo dye (38, 61). It is highly probable that there is a methylene group joined to the benzene ring. When *O,O',N*-triacetyldihydroveratramine (XXXI) is oxidized with chromic acid there is formed a keto compound, $C_{33}H_{45}O_6N$, presumably by the conversion of a methylene into a carbonyl, formulated as LIV. The UV-absorption spectrum of this compound indicates a carbonyl conjugated with the benzene ring, but it is not identical with a degradation product of jervine to which the same structure has been

assigned (61).*



XXX $R_1 = R_2 = R_3 = H$

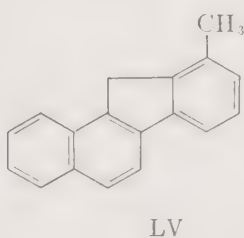
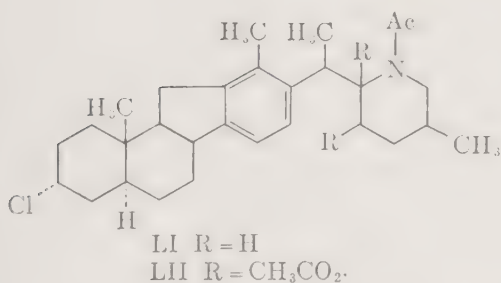
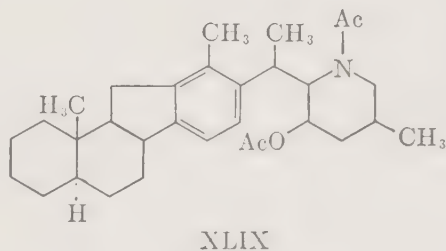
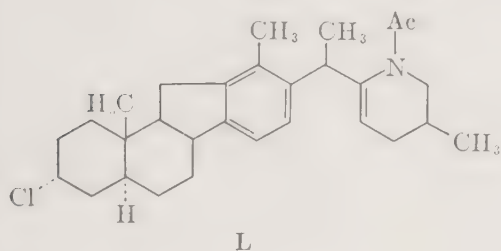
XXXI $R_1 = R_2 = R_3 = CH_3CO$

XXXII $R_1 = R_2 = H$ $R_3 = CH_3CO$

XLVI $R_1 = CH_3C_6H_4SO_2$ $R_2 = H$ $R_3 = CH_3CO$

XLVII $R_1 = R_2 = CH_3CO$

XLVIII $R_1 = H$ $R_2 = CH_3CO$



The position of the sluggishly reactive hydroxyl is indicated by the products obtained in the selenium dehydrogenation of veratramine. There was obtained 3-methyl-5-hydroxypyridine, identical with a synthetic specimen (41, 42). There were also obtained a hydrocarbon,

* Wintersteiner and Hosansky, *J. Am. Chem. Soc.*, **74**, 4474 (1952) obtained LIV by catalytic hydrogenation of LXXVII from jervine and correlated thus the two alkalines.

TABLE 10
PROPERTIES OF VERATRAMINE AND ITS DERIVATIVES

Compound	Formula	M.p. °C.	$[\alpha]_D$	Ref.
Veratramine (XXVII) ^a	$C_{27}H_{39}O_2N$	209.5-210.5, 206-207	-70° (CH ₃ OH), -71° (CHCl ₃)	38, 56, 61
Hydrochloride Picrate		310		
N-Methylveratramine methiodide		217.5-218		38, 56, 61
N-Methylveratramine methochloride		268 (dec)		38, 56, 61
O,O',N-Triacetylveratramine (XXVIII)	$C_{33}H_{45}O_5N$	277		56
N-Acetylveratramine (XXIX)	$C_{29}H_{41}O_3N$	204-206, 205-206.5	+39° (CH ₃ OH)	56, 61
Dihydroveratramine (XXX)	$C_{27}H_{41}O_2N$	179-180		36, 56
		192.5-194, 197-198, 198-200	+26° (CHCl ₃)	36, 56, 61
O,O',N-Triacetyldihydroveratramine (XXXI) ^b	$C_{33}H_{47}O_5N$	189.5-190.5	+84° (CHCl ₃)	61
N-Acetyldihydroveratramine (XXXII)	$C_{29}H_{43}O_3N$	220-223	+81° (CHCl ₃)	61
Nitration product of O,O',N-triacetyl- dihydroveratramine (LIII) ^c	$C_{33}H_{46}O_7N_2$	238-239	263° (CHCl ₃)	61
Amino-O,O',N-triacetyldihydroveratramine ^d	$C_{33}H_{45}O_6N$	amorph.	+59° (CHCl ₃)	61
O,O',N-Triacetylketodihydroveratramine (LIV) ^e	$C_{33}H_{43}O_6N$	241-245 after sintering and darkening at 238	+81° (CHCl ₃) +43° (CHCl ₃)	61
O,O',O'',N-Tetracetyl compound (XXXIII) ^f	$C_{33}H_{49}O_8N$	156-157	+33° (CHCl ₃)	42
"α"-Triacetylepoxide (XXXIV)	$C_{33}H_{45}O_6N$	208-211		
"β"-Triacetylepoxide } (XXXV) or N-Acetylepoxide (XXXVI)	$C_{29}H_{41}O_4N$	198-199 167-172		
O,O',N-Triacetyldihydroxydihydroveratramine (XXXVII)	$C_{33}H_{47}O_7N$	281-284	+51.3° (CHCl ₃)	42
O,O',O'',N-Tetracetyl derivative of dihydroxy- dihydroveratramine (XXXVIII)	$C_{33}H_{49}O_8N$	167-172		42
O,O',O'',N-Tetracetyl compound (XXXIX) (Tetracetyl-6-hydroxy-Δ ⁴ -veratramine)	$C_{35}H_{47}O_7N$	247-252		42
O,O'-Diacetyl-N-ethylhydroxydihydrovera- tramine (XI) (N-Ethyl-5-hydroxydihydro- veratramine 3,23-diacetate)	$C_{33}H_{49}O_5N$	178-182	+40° (CHCl ₃)	42
O,O'-Diacetyl-N-ethylveratramine (XLI), or isomer with other position of double bond	$C_{33}H_{47}O_4N$	164-168 198-205		42
Hydrochloride				42

<i>O,O'</i> -Diacetyl- <i>N</i> -ethylidihydroxydihydroveratramine (NLIH)	$C_{33}H_{49}O_6N$	221.5-226.5	+24° (CHCl ₃)	42
α,β -Unsaturated ketone (NLIH) (Δ^4 -Veratramine-3-one)	$C_{27}H_{37}O_2N$	amorph.	+69° (C ₂ H ₅ OH)	42, 61
Hydrochloride		amorph.		61
Oxime		249-251 (dec)		61
<i>N</i> -Acetyl derivative of α,β -unsaturated ketone ^a	$C_{29}H_{39}O_3N$	262-264		61
Oxime	$C_{35}H_{43}O_6N$	252-255		
2,4-Dinitrophenylhydrazones				
Mixture of epimeric α,β -unsaturated alcohols (NLIIV and NLI V) (Δ^4 -Veratramine)	$C_{27}H_{39}O_2N$	129-131.5 or 124-127	+40° (C ₂ H ₅ OH)	42
Hydrochloride		123-125	+54° (C ₂ H ₅ OH), +53.6° (CHCl ₃)	42
Hydroxyketone (Dihydroveratramine-3-one)	$C_{27}H_{39}O_2N$	194-215 not sharp, a portion only melts at 260-270		42
Oxime hydrochloride				
<i>N</i> -Acetyl derivative of the hydroxyketone	$C_{27}H_{39}O_2N$	191-194		42
<i>O,N</i> -Diacetyl derivative of the hydroxyketone	$C_{31}H_{43}O_4N$	amorph.		42
Diketone (dihydroveratramine-3,23-dione)	$C_{27}H_{37}O_2N$	116-122.5		61
<i>N</i> -Acetyl derivative of the diketone $C_{27}H_{37}O_2N^h$	$C_{29}H_{39}O_3N$	264-267		42, 61
Monotosylate of <i>N</i> -acetyldihydroveratramine (NLI VI)	$C_{36}H_{49}O_5NS$	167.5-168.5	+53° (CHCl ₃)	61
<i>O</i> -Tosyl- <i>O'</i> - <i>N'</i> -diacetyldihydroveratramine	$C_{38}H_{51}O_6NS \cdot \frac{1}{2}H_2O$	168-169	+74° (CHCl ₃)	61
Compound $C_{31}H_{43}O_3N$ (NLI VII)		208-210	+10° (CHCl ₃)	61
Compound $C_{29}H_{41}O_2N$ (NLI VIII)		224-226	+108° (CHCl ₃)	61
Compound $C_{31}H_{45}O_3N$ (NLI IX)		204-205	+99° (CHCl ₃)	61
Compound $C_{29}H_{40}ONCl^i$ (I)		205-206 (dec)	+178° (CHCl ₃)	61
Compound $C_{29}H_{42}ONCl$ (LI)		178.5-180	+65° (CHCl ₃)	61
Triacetyl derivative (LII)	$C_{33}H_{46}O_5NCl$	210-211	+74° (CHCl ₃)	61

^a λ_{max} , 268 μ (log ϵ 2.8) (C₂H₅OH); digitonin precipitable. ^b λ_{max} , 269 μ (log ϵ 2.8) (C₂H₅OH). ^c λ_{max} , 280, 270, 260 μ (log ϵ 3.61) (C₂H₅OH).
^d λ_{max} , ca. 295 μ (log ϵ 3.3) (C₂H₅OH); λ_{max} , ca. 270 μ (log ϵ 2.8) (3.5% ethanolic hydrochloric acid).
^e λ_{max} , 251 μ (log ϵ 4.03) (C₂H₅OH); IR-absorption spectrum bands at 5.75, 5.87, 6.08 μ (Nujol); does not form a 2,4-dinitrophenylhydrazone.
^f λ_{max} , 268 μ (log ϵ 2.7) (C₂H₅OH); IR-absorption spectrum bands at 3.08, 5.78 and 6.16 μ (Nujol). ^g IR-absorption bands at 2.88 and 6.11 μ (Nujol).
^h λ_{max} , 268 μ (log ϵ 2.77) and 305 μ (log ϵ 2.36) (methanol-chloroform); IR-absorption spectrum bands at 5.87 and 6.18 μ (Nujol).
ⁱ λ_{max} , 269 μ (log ϵ 2.7).

$C_{22}H_{20}$ (or $C_{20}H_{18}$), a base melting at 224–227° and a phenolic base melting at 248–250°. The hydrocarbon was identical with one similarly obtained from jervine (p. 297) and had a UV-spectrum indicating a 1,2-benzofluorene derivative. It has been suggested that it is a homologue of LV (41).

The reactions described above are satisfactorily explicable on the basis of structure XXVII for veratramine. On this basis its relation to other *Veratrum* and *Solanum* alkaloids and to the steroids is obvious. Further, a comparison of the optical activities of analogous compounds in the *Veratrum* and steroid series indicates structural and configurative analogies. For example, change of veratramine to its dihydro derivative is accompanied by a strong positive change of rotation, a change well known in many steroids. The plausible location of one of the hydroxyls at position 3 in ring A and with it the β,γ -double bond between carbons 5 and 6 thus receives strong confirmation. Since veratramine and its dihydro derivative form sparingly soluble digitonides, it is highly probable that the hydroxyl at position 3 has the β -configuration.

On the basis of the formation of a benzofluorene derivative on dehydrogenation of veratramine it can be assumed that rings A and B are six-membered and the benzene nucleus must be regarded as the D ring. Furthermore, the formation of the fluorene derivative LV indicates that ring C is five-membered. Finally, the placing of the four methyl groups at positions 10, 17, 20, and 26 is in accord with their positions in known steroids.

d. Jervine.

ISOLATION. The powdered roots of *V. album* are digested for several days with ethanol and the extract evaporated under a water pump vacuum at 50°. The residue is dissolved in water, thoroughly extracted with hexane, and filtered to remove insoluble resins. The clear filtrate is then treated with 6*N* ammonium carbonate solution and the precipitate separated by filtration, washed with water, dried, and recrystallized from carbon tetrachloride. The jervine thus obtained is then conveniently recrystallized from methanol (54). Jervine may also be obtained from *V. viride* (p. 282).

REACTIONS AND STRUCTURE. Jervine, $C_{27}H_{39}O_3N$, has recently been subjected to intensive chemical investigations because of the possibility of obtaining from it nitrogen-free steroids with an oxygen substituent at position 11. The structure LVI recently submitted by Fried and co-workers (20) will be used in the following discussion and indicates that the hoped-for steroids will not be readily available from it.

Jervine has one secondary hydroxyl, a sluggishly reactive α,β -unsaturated carbonyl, and ether oxygen, and a basic secondary nitrogen. There is present also a second double bond and hence jervine is hexacyclic.

Jervine forms crystalline salts with hydrogen halides, and with nitrous acid a neutral *N*-nitroso derivative, $C_{27}H_{38}O_4N_2$, is formed. When heated with acetic anhydride an *O,N*-diacetyl (LVIII) and an *N*-acetyl derivative (LVII) are obtained. The monoacetyl derivative on treatment with benzoyl chloride in pyridine forms an *O*-benzoyl-*N*-acetyl-jervine (LIX) (33, 40).

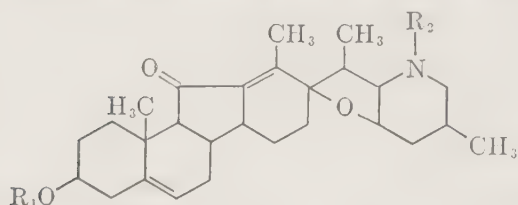
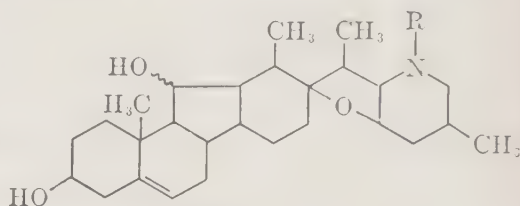
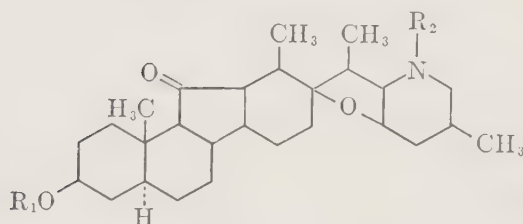
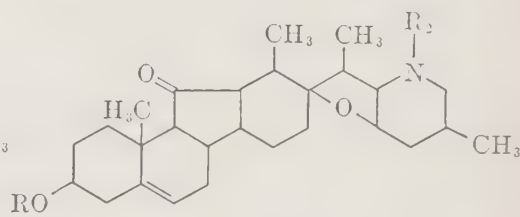
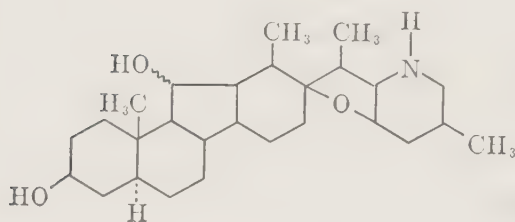
Catalytic hydrogenation with platinum under alkaline conditions serves to reduce selectively the double bond which is conjugated with the carbonyl to generate dihydrojervine (LX). This too forms an *O,N*-diacetyl derivative (LXI), which can be partially hydrolyzed to an *N*-acetyl derivative (LXII) (2, 39). Catalytic reduction of either jervine (LVI) or dihydrojervine (LX) with platinum in acetic acid saturates both double bonds with the formation of tetrahydrojervine (LXIII), which was characterized as its *N*-nitroso derivative and a sparingly soluble sulfate. When it is treated with acetic anhydride followed by alkaline hydrolysis there results *N*-acetyltetrahydrojervine (LXIV) (33, 39).

When jervine is reduced with sodium and butanol there is formed " α "-dihydrojervinol (LXV), melting at $223-225^\circ$, which was at one time described as tetrahydrojervine. This compound on acetylation followed by alkaline hydrolysis yields the *N*-acetyl derivative (LXVI). When dihydrojervine is reduced with sodium and butanol an isomer of LXV, the " β "-dihydrojervinol (LXVII) melting at $286-289^\circ$, is obtained which with acetic anhydride furnishes an *O,O',N*-triacetyl derivative (LXVIII). In the presence of a platinum catalyst in acetic acid the substance LXVII is reducible to a tetrahydrojervinol (LXIX) that is also obtainable by the reduction of tetrahydrojervine (LXIII) with sodium and butanol (33, 39, 40).

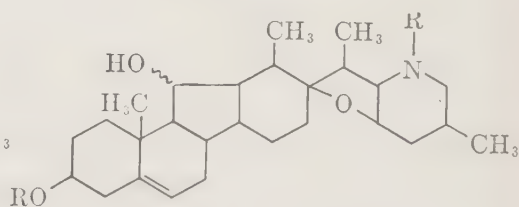
When jervine is oxidized with acetone and aluminum *tert*-butoxide or when heated with copper powder it yields a diketone, Δ^4 -jervone (LXX) in which there are two α,β -unsaturated carbonyls, only one of which reacts with hydroxylamine. Similarly, dihydrojervine (LX) on Oppenauer oxidation yields a diketone, Δ^4 -dihydrojervone (LXXI) in which only one carbonyl is α,β -unsaturated and only one carbonyl reacts with hydroxylamine. Under similar conditions β -dihydrojervinol (LXV-III) is convertible into an α,β -unsaturated ketone, Δ^4 - β -dihydrojervonol (LXXII) (39, 40).

The doubly unsaturated diketone LXX on Meerwein-Ponndorf reduction affords a keto alcohol, Δ^4 -jervine (LXXIII), which is probably not homogeneous, and in which the hydroxyl in ring A is probably of the allyl type because of its positive Rosenheim test. The second α,β -unsaturated carbonyl is not reduced in this reaction. Under similar condi-

tions, however, the α,β -unsaturated keto alcohol LXXII gives rise to a mixture of epimers of the composition $C_{27}H_{43}O_3N$ (39, 40). Consequently, it is assumed in analogy with other *Solanum* and *Veratrum* alkaloids that the above oxidation and reduction reactions indicate a β,γ -double bond in ring B to the oxygen function at position 3 in ring A.

LVI $R_1 = R_2 = H$ LVII $R_1 = H$ $R_2 = CH_3CO$ LVIII $R_1 = R_2 = CH_3CO$ LIX $R_1 = PhCO$ $R_2 = CH_3CO$ LXV $R = H$ LXVI $R = CH_3CO$ LXIII $R_1 = R_2 = H$ LXIV $R_1 = H$ $R_2 = CH_3CO$ LX $R_1 = R_2 = H$ LXI $R_1 = R_2 = CH_3CO$ LXII $R_1 = H$ $R_2 = CH_3CO$ 

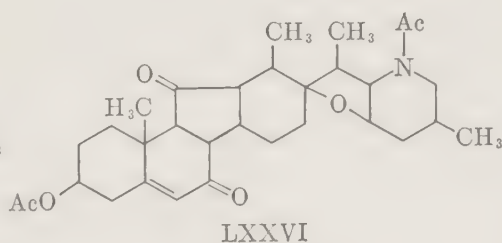
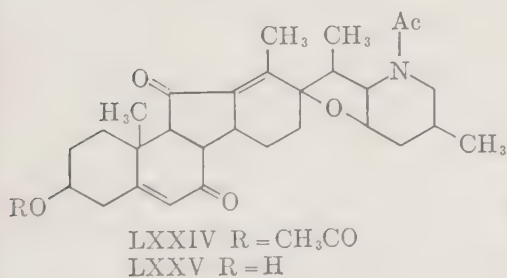
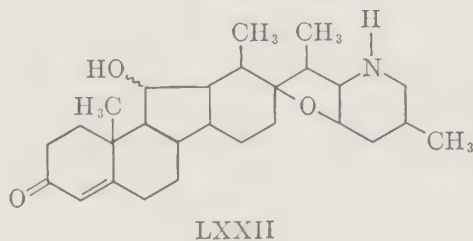
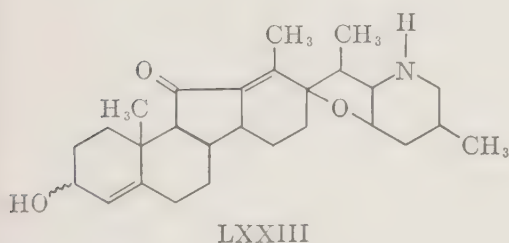
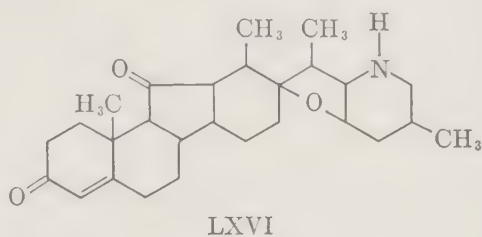
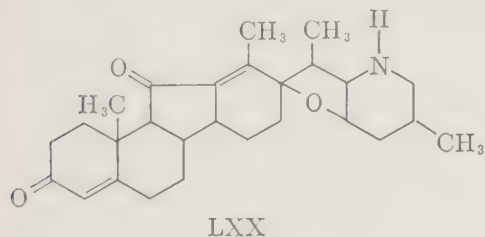
LXIX

LXVII $R = H$ LXVIII $R = CH_3CO$

A new carbonyl in conjugation with the double bond can be introduced by the chromic acid oxidation of *O,N*-diacetyljervine (LVIII) to yield the *O,N*-diacetyl diketo compound LXXIV in which both carbonyls are α,β -unsaturated. The carbonyl located in ring B thus introduced reacts readily with carbonyl reagents such as semicarbazide and 2,4-dinitrophenylhydrazine. In a similar manner, *O,N*-diacetyldihydrojervine (LXI) yields the analogous oxidation product LXXVI (64).

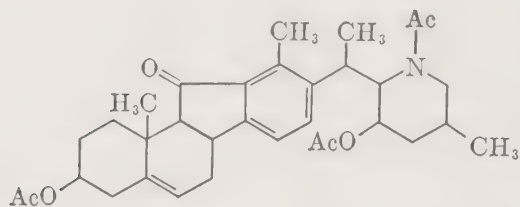
Treatment of *O,N*-diacetyljervine (LVIII) with sulfuric acid in acetic anhydride-acetic acid generates an *O,O',N*-triacetyl derivative,

$C_{33}H_{43}O_6N$ (LXXVII), whose UV-spectrum indicates an aromatic ring in conjugation with a carbonyl. This compound on catalytic reduction, then alkaline hydrolysis, and finally, chromic acid oxidation of the intermediate dihydroxy ketone, yields the triketone LXXVIII. It follows therefore that the sulfuric acid treatment of *O,N*-diacetyljervine effects scission of the oxide ring generating a double bond and a hydroxyl group. The intermediate, regarded as a cyclohexadiene derivative, suffered conversion to the aromatic compound LXXVII either by disproportionation or by dehydrogenation with the sulfuric acid (20, 66).

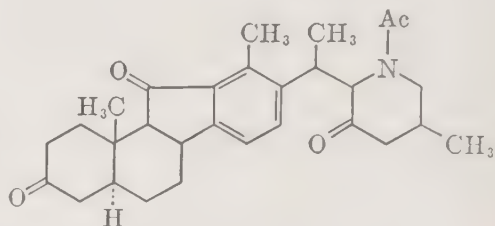


Tetrahydrojervine (LXIII) also gives rise to a product, the *O,O',N*-triacetyl derivative (LXXIX), whose formation is dependent upon ring scission and the formation of a double bond and a new hydroxyl, by treatment with sulfuric acid in acetic anhydride-acetic acid. This upon alkaline saponification gives rise to the *N*-acetyl compound LXXX, which on reacylation gives rise to an isomer of LXXIX, namely, the triacetyl compound LXXXI. This isomerization is probably due to the shift of the newly introduced double bond. The compound LXXIX can be catalytically hydrogenated to the dihydro derivative LXXXII, whereas

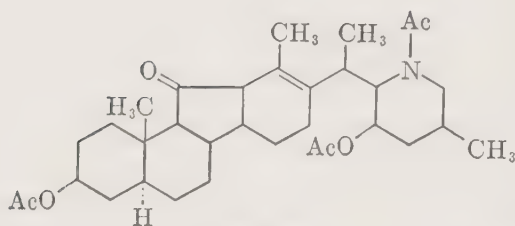
the isomer, LXXXI, yields a mixture from which it was possible to separate chromatographically another isomeric dihydro derivative, presumably LXXXIII (66).



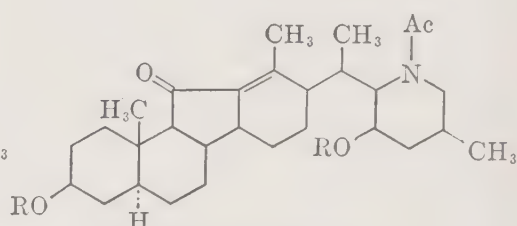
LXXVII



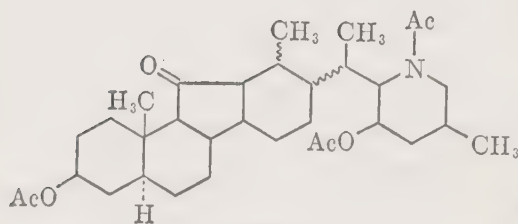
LXXVIII



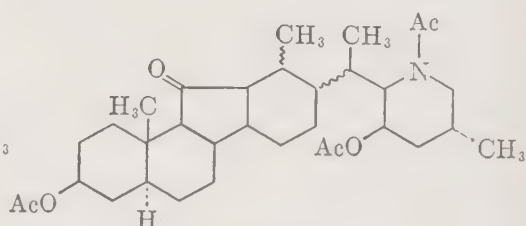
LXXIX



LXXX R = H
LXXXI R = CH₃CO



LXXXII



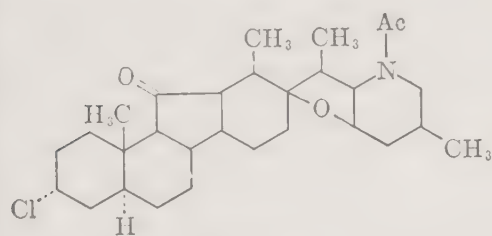
LXXXIII

When *N*-acetyltetrahydrojervine (LXIV) is reacted with phosphorus pentachloride a desoxychloro derivative (LXXXIV) is formed which on ring scission with sulfuric acid in acetic anhydride-acetic acid gives rise to the *O,N*-diacetyl compound LXXXV. This on partial hydrolysis with alkali affords an *N*-acetyl compound (LXXXVI) which on reacylation yields an isomeric diacetyl derivative (LXXXVII) in analogy with similar reactions of tetrahydrojervine. The *N*-acetyl derivative (LXXXVI) on chromic acid oxidation formed a ketone (LXXXVIII) with a reactive carbonyl (66).

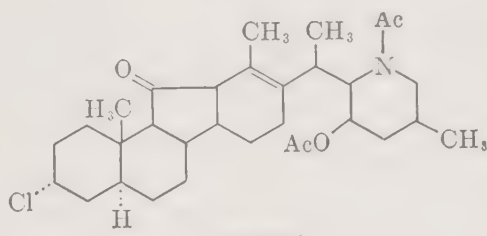
While the reactions of jervine and its derivatives with sulfuric acid in acetic anhydride-acetic acid yield products whose formation can be plausibly explained, the reaction of jervine with methanolic hydrochloric

acid yields isojervine, $C_{27}H_{39}O_3N$, whose structure remains in doubt. Isojervine is unstable toward alkali, but the changes which occur under these conditions are not understood. The presence of an NH group in isojervine can be demonstrated by the formation of an *N*-acetyl derivative, $C_{29}H_{41}O_4N$. When isojervine is subjected to energetic reaction with acetic anhydride a triacetyl derivative, $C_{33}H_{45}O_6N$, is formed (36, 39).

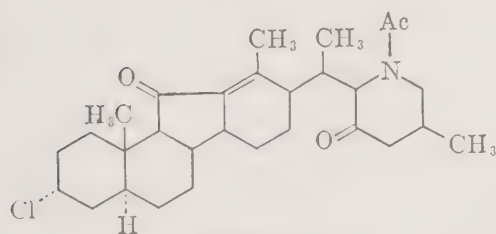
Reduction of isojervine in methanol in the presence of a platinum catalyst affords the compound $C_{27}H_{45(47)}O_2N$, whereas sodium in butanol generates dihydroisojervinol $C_{27}H_{43}O_3N$ (39).



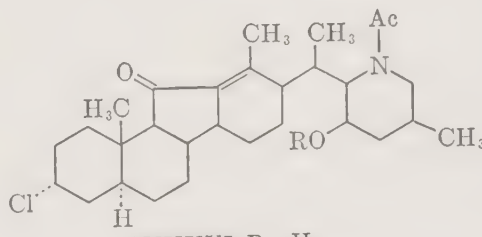
LXXXIV



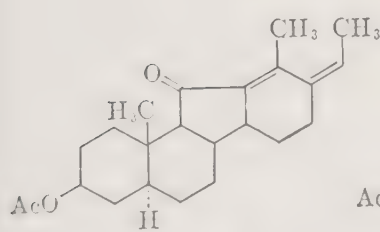
LXXXV



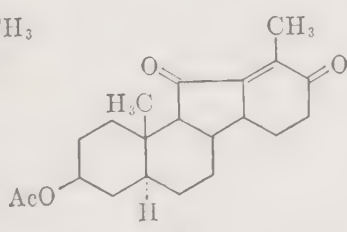
LXXXVIII



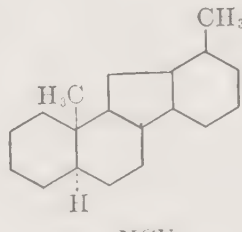
LXXXVI R = H

LXXXVII R = CH_3CO 

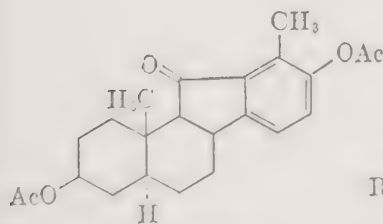
LXXXIX



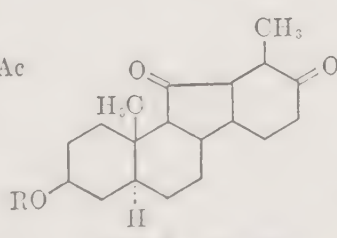
XC



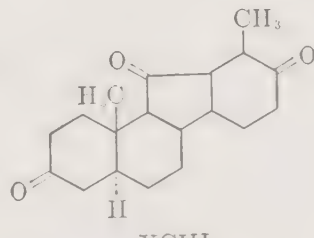
XCV



XCIV

XCI R = CH_3CO

XCII R = H

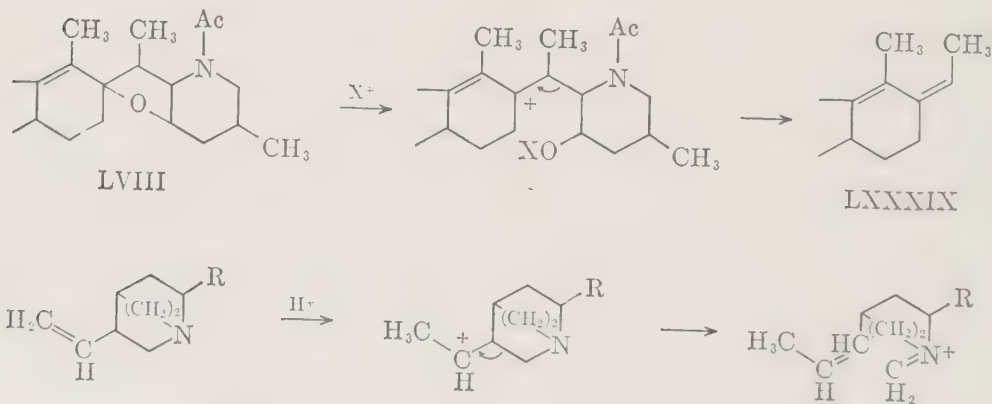


XCIII

A remarkable scission reaction takes place when jervine is heated to 140° with acetic anhydride and zinc chloride. A portion of the molecule that contains six carbons, the nitrogen, and the ring oxygen, is split off. It is possible to isolate from the reaction mixture a nitrogen-free substance, $C_{23}H_{30}O_3$ (LXXXIX), whose UV-spectrum indicates a conjugated doubly unsaturated carbonyl, which has an acetoxy group, and is capable of reduction to a hexahydro derivative melting at $112-114^\circ$. Oxidation of the compound LXXXIX with chromic acid removes two more carbons to yield an unsaturated 1,4-diketone, $C_{21}H_{26}O_4$ (XC) with one reactive carbonyl. The double bond in this compound is susceptible to reduction with zinc and acetic acid (62), whereby a dihydro compound, $C_{21}H_{28}O_4$ (XCI) is formed. Alkaline hydrolysis of the acetoxy diketone (XCI) affords the hydroxy diketone XCII, which may be oxidized to the triketone, $C_{19}H_{22}O_3$ (XCIII) (20). Prolonged treatment of the diketone (XC) with alkali generates a phenolic substance which was isolated as its diacetate, $C_{23}H_{26}O_5$ (XCIV). This compound has a nonreactive carbonyl, and it is therefore assumed that the phenolic hydroxyl had its origin in the reactive carbonyl of XC (20).

Finally, when the acetoxy diketone (XC) is catalytically reduced, the reduction product saponified, and the last substance reduced by Clemmensen's method, there is obtained a saturated tetracyclic hydrocarbon, $C_{19}H_{32}$ (XCV) (20).

The characteristic scission reaction by which compound LXXXIX is obtained is explicable in analogy with the long-known and recently explained scission of niquidine (49, 67) and is given schematically below. If this interpretation is correct it offers substantiation of the mooted 1,3-positions of the nitrogen and the ring oxygen.



The dehydrogenation of jervine and of isojervine yields 2-ethyl-5-methylpyridine as well as a hydroxypyridine, $C_8H_{11}ON$, which is regarded as 3-hydroxy-2-ethyl-5-methylpyridine (31, 41).

The neutral dehydrogenation products were separable chromatographically and by distillation into a number of products. The following compounds were recorded without however adequate proof of their homogeneity or composition: (a) $C_{14}H_{14}$, (b) $C_{20}H_{22}$, (c) $C_{20}H_{16}$, (d) $C_{21}H_{24}$, (e) $C_{24}H_{30}$, (f) $C_{22}H_{20}$, (g) $C_{21}H_{18}$, and (h) $C_{20}H_{22}O$. The hydrocarbon (a) exhibits an absorption spectrum identical with that of 5,6-benzohydrindene. Hydrocarbons (b) and (e) exhibit spectra indicating fluorene derivatives. Hydrocarbon (c) has a spectrum similar to that of 1,2-benzofluorene, whereas the compounds (f), (g), and (h) appear to be derivatives of β -phenylnaphthalene (31).

When jervine is distilled with soda-lime a crystalline base, $C_8H_{17}ON$, is obtained representing ring F, which may be the hexahydro derivative of the dehydrogenation product $C_8H_{11}ON$ (31).*

e. Cevagenine. Mild alkaline hydrolysis of veratridine, as recently shown by Stoll and Seebeck (60a), yields the alkamine cevagenine, $C_{27}H_{43}O_8N$, which on further treatment with alkali is isomerized to cevine. Cevagenine is also obtainable from the ester-alkaloid cevadine. It yields well-crystallizable salts with perchloric and thiocyanic acids, and forms an *N*-oxide and a triacetyl derivative, $C_{33}H_{49}O_{11}N$. The IR-absorption spectrum shows the presence of a carbonyl capable of forming an oxime.

f. Cevine. ISOLATION. Vigorous treatment of cevadine with alkali yields cevine and angelic acid as well as tiglic acid while similar treatment of veratridine yields cevine and veratric acid, the cevine being a secondary product resulting from the action of alkali on the primary cevagenine (60a).

REACTIONS AND STRUCTURE. The determination of the structures of those *Veratrum* alkaloids that have a large number of oxygen atoms offers considerable difficulty. Of these cevine has been the most thoroughly investigated, but it has not been possible to propose a satisfactory structure for it.

The correct empirical formula of cevine, $C_{27}H_{43}O_8N$, has long been known from the analyses of amorphous material and has later been substantiated by the analysis of the crystalline alkaloid. Cevine is a weak tertiary base, $pK'_A = 9.48$. It forms a hydrochloride, $C_{27}H_{43}O_8N \cdot HCl$, and a methiodide, $C_{27}H_{43}O_8N \cdot CH_3I$, which latter on treatment with silver chloride is convertible to the corresponding methochloride. It also yields characteristic salts when reacted with alkali hydroxides in alcoholic solutions, the cevine potassium salt, $C_{27}H_{42}O_8NK \cdot KOC_2H_5$ having been described. With hydrogen peroxide it reacts to form an *N*-oxide, $C_{27}H_{43}O_9N$, which was characterized as hydrochloride and aurichloride (16, 17, 22, 30, 68).

* For addtl. information on oxygen functions in cevagenine and cevine see E. Seebeck and A. Stoll, *Helv. Chim. Acta*, **35**, 1942 (1952), *ibid.*, **36**, 189 (1953) and D. R. H. Barton and J. F. Eastham, *J. Chem. Soc.*, **953**, 424.

TABLE 11
PROPERTIES OF JERVINE AND ITS DERIVATIVES

Compound	Formula	M.p. °C.	$[\alpha]_D$	Ref.
Jervine (LVI) ^a	C ₂₇ H ₃₉ O ₃ N	237-238, 243.5-244.5, 244-246	-147°, -150° (C ₂ H ₅ OH)	33, 39, 52 53, 54, 69
Hydrochloride		330-334 (dec)		
Hydriodide		302-305		
Sulfate		297-298		
Nitrate				
Trichloracetate		243-244		
N-Nitroso derivative	C ₂₇ H ₃₁ O ₄ N ₂	250-253 (dec)		33
Di-(<i>p</i> -bromobenzoyl)jervine	C ₄₁ H ₄₅ O ₈ NBr ₂	280-282 (dec)		52
N-Acetyljervine (LVII)	C ₂₉ H ₄₁ O ₄ N	224-225		33
O,N-Diacetyljervine (LVIII)	C ₃₁ H ₄₃ O ₅ N	154-163, 162-164		33
N-Acetyl-O-benzoyljervine (LIX)	C ₃₆ H ₄₅ O ₆ N	219-223		40
Dihydrojervine (LX)	C ₂₇ H ₄₁ O ₃ N	248-251	-82° (C ₂ H ₅ OH)	2, 39
O,N-Diacetyldihydrojervine (LXI)	C ₃₁ H ₄₅ O ₅ N	210-212		39
N-Acetyldihydrojervine (LXII)	C ₂₉ H ₄₃ O ₄ N	157-159, solidifies and remelts at 256-259		39
Tetrahydrojervine (LXIII)	C ₂₇ H ₄₃ O ₃ N	216-221, sinters at 213 above 360	-18° (C ₂ H ₅ OH)	39, 55 39, 55
Hydrochloride				39
N-Acetyltetrahydrojervine (LXIV)	C ₂₉ H ₄₅ O ₄ N	266-269		33, 39
"α"-Dihydrojervinol (LXV)	C ₂₇ H ₄₃ O ₃ N	223-225	-107° (C ₂ H ₅ OH)	39
N-Acetyl-"α"-dihydrojervinol (LXVI)	C ₂₉ H ₄₅ O ₄ N	150-151		39
"β"-Dihydrojervinol (LXVII)	C ₂₇ H ₄₃ O ₃ N	286-289	-4° (C ₂ H ₅ OH)	39
O,O',N-Triacetyl-"β"-dihydrojervinol (LXVIII)	C ₃₃ H ₄₉ O ₆ N	254-257		40
Tetrahydrojervinol (LXIX)	C ₂₇ H ₄₅ O ₃ N	293-296	+48.5° (C ₂ H ₅ OH)	39
Diketone (Δ ⁴ -Jervone) (LXX)	C ₂₇ H ₃₇ O ₃ N	193-194	+28° (C ₂ H ₅ OH)	39
(Oxime	C ₂₇ H ₃₈ O ₃ N ₂	287-289		39

TABLE 11 (Continued)

Compound	Formula	M.p. °C.	$[\alpha]_D$	Ref.
Diketone (Δ^4 -Dihydrojervone) (LXXI)	$C_{27}H_{39}O_3N$	131-132		40
Oxime	$C_{27}H_{40}O_3N_2$	293-297		40
Compound $C_{27}H_{41}O_3N$ (Δ^4 - β -Dihydrojervonol) (LXXII)		221.5-223.5		40
Oxime	$C_{27}H_{42}O_3N_2$	286-292		40
Compound $C_{27}H_{39}O_3N$ (Δ^4 -Jervine) (LXXIII)		203-211, sinters at 185°		39
Mixture of epimeric alcohols (Δ^4 - β -Dihydrojervinol) Hydrochloride	$C_{27}H_{43}O_3N$	246-248	+54.5° (CHCl ₃)	40
		272-275		40
Compound $C_{31}H_{41}O_6N$ (LXXIV)		237-239	-165° (C ₂ H ₅ OH)	64
Semicarbazone	$C_{32}H_{44}O_6N_4$	245-255 (dec)		64
2,4-dinitrophenylhydrazone	$C_{37}H_{45}O_9N_5$	293-298		64
Compound $C_{29}H_{39}O_5N$ (LXXV)		262-264	-192° (CHCl ₃)	64
Compound $C_{31}H_{43}O_6N$ (LXXVI)		281-284	-116° (CHCl ₃)	64

^a λ_{max} , 250 m μ (log ϵ 4.2) (C₂H₅OH); 4 active hydrogens.

TABLE 12
 PROPERTIES OF CEVAGENINE AND ITS DERIVATIVES

Compound	Formula	M.p. °C.	$[\alpha]_D$	Ref.
Cevagenine ^a	$C_{27}H_{43}O_8N$	241–242 (dec)	-47.8° (C_2H_5OH)	60a
Perchlorate		199–201 (dec)		
Thiocyanate		263–265 (dec)		60a
Oxime		248–249 (dec)		60a
Cevagenine <i>N</i> -oxide		217–220 (dec)		
Triacetylcevagenine	$C_{33}H_{49}O_{11}N$	248–249 (dec)		60a

^a IR-absorption spectrum shows a carbonyl band at 1707 cm^{-1} (Nujol paste).

Four of the eight oxygens are present as hydroxyls. A dibenzoylcevaine, $C_{41}H_{51}O_{10}N$, which yields a crystalline benzoate, a hydrochloride hydrate, a nitrate, and an acetate, is known. A di-(*o*-nitrobenzoyl)cevaine and a diacetylcevaine are also described, while vigorous reactions with acetic anhydride-perchloric acid gives rise to a tetracetylcevaine, $C_{35}H_{51}O_{12}N \cdot H_2O$. The functions of the four other nonreactive oxygens is unknown, but the IR-absorption spectrum indicates that this alkaloid, contrary to the observations on cevagenine, does not have a carbonyl (17, 43, 46, 47, 60a).

Cevaine is not hydrogenated in alcoholic solution with a platinum catalyst, but reduction with Raney nickel affords a dihydro derivative, $C_{27}H_{45}O_8N$. A substance, possibly identical with the latter, is obtained by sodium and butanol reduction as well as another containing one less oxygen, $C_{27}H_{43}O_7N$ (30, 43).

On treatment with alkali cevaine is changed to the so-called β -cevaine which Jaffe and Jacobs (43) interpret as an allyl alcohol \rightarrow enol change.

On the basis of the above data it follows that cevaine is hexacyclic or pentacyclic with a double bond. The available information concerning its structure has been obtained from experiments on selenium dehydrogenation, zinc-dust distillation, soda-lime distillation, and chromic acid oxidation.

SELENIUM DEHYDROGENATION. A large number of products have been separated from the reaction mixture. The following basic substances were obtained:

- (a) β -Picoline.
- (b) 2-Ethyl-5-methylpyridine.
- (c) Base, C_8H_9ON ; picrate, m.p. 150–151°.
- (d) Base, $C_8H_{11}ON$.
- (e) Base, $C_9H_{13}N$; picrate, m.p. 150–151°.
- (f) Base, $C_{20}H_{19}N$, m.p. 233–235°.
- (g) Base, $C_{24}H_{25}N$ ($C_{23}H_{23}N$), m.p. 186°.

- (h) Base, $C_{25}H_{25}N$ ($C_{26}H_{25}N$), m.p. 229–230°.
- (i) Cevanthridine, $C_{25}H_{27}N$, m.p. 211–212°.

The last-named was further examined. It is a tertiary base which yields a crystalline hydrochloride, a picrate, and a methiodide. Hydrogenation converts it to tetrahydrocevanthridine, $C_{25}H_{31}N$, which was characterized as a secondary base by the formation of an acetyl derivative, $C_{27}H_{33}ON$, and a *p*-brombenzoyl derivative, $C_{32}H_{34}ONBr$.

From the neutral fraction the following hydrocarbons were isolated:

- (a) $C_{13}H_{12}$, liquid, identical with 1,2-benzohydrindane.
- (b) $C_{17}H_{16}$, solid.
- (c) $C_{18}H_{18}$, m.p. 116–118°.
- (d) $C_{19}H_{20}$, m.p. 185–188°.
- (e) $C_{24}H_{30}$, m.p. 108–110°.

The hydrocarbons (b) to (e) show UV-absorption spectra similar to that of fluorene.

Two oxygen-containing compounds were also separated from the neutral fraction: (a) cevanthrol, $C_{17}H_{16}O$, an alcohol which forms an acetyl derivative, $C_{18}H_{18}O_2$, and (b) an apparently nonhomogeneous product, $C_{23}H_{24}O$, melting at 181–187° (3, 4, 5, 8, 9, 10).

ZINC-DUST DISTILLATION. The products of this reaction, during which the mixture was heated to 360°, and then subsequently reduced catalytically in acetic acid with platinum were the following:

- (a) β -Pipecoline, $C_6H_{13}N$; hydrochloride, m.p. 171°; 3,5-dinitrobenzoyl, m.p. 111–113°.
- (b) Base, $C_7H_{13-15}N$, liquid; picrate, m.p. 178–180°.
- (c) Base, $C_7H_{15}N$, liquid; picrate, m.p. 171–176°; $[\alpha]_D + 9.7^\circ$; presumably *N*-methyl- β -pipecoline.
- (d) 2-Ethyl-5-methylpyridine, $C_8H_{11}N$; picrate, m.p. 128–133°.
- (e) Base, $C_9H_{13}N$; picrate, m.p. 150–152° (27, 28).

SODA-LIME DISTILLATION. The volatile reaction products were also reduced catalytically with platinum in acetic acid and the following bases are worthy of mention:

- (a) β -Pipecoline; isolated as its 3,5-dinitrobenzoyl derivative with $[\alpha]_D + 8^\circ$ (acetone) and therefore partly racemic.
- (b) Base, $C_8H_{19}N$, liquid; 3,5-dinitrobenzoyl derivative, m.p. 100–110°, $[\alpha]_D + 11.7^\circ$ (acetone); probably 2-ethyl-5-methylpiperidine.
- (c) Tertiary base, $C_{10}H_{19}N$; picrate, m.p. 142–150°. This base does not have *N*-methyl and forms a methiodide which could be carried through two stages of the Hofmann degradation.
- (d) Tertiary base, $C_{10}H_{17}N$; picrate, m.p. 118–120°; convertible by further hydrogenation to base (c).

In addition to the above bases two nitrogen-free ketonic compounds, isolated as their semicarbazones, were obtained, namely: a semicarbazone of the ketone $C_7H_{12}O$, m.p. 217–219°, and a semicarbazone of the ketone $C_{11}H_{18}O$, m.p. 160–170° (27, 28, 29).

The so-called cevine betaine, which is identical with "desmethyl-cevine," obtained by reacting cevine methohalides with silver oxide, was also subjected to soda-lime distillation followed by catalytic reduction. The main product was a base, $C_9H_{19}ON$, which yielded a methiodide, $C_9H_{19}ON \cdot CH_3I$, melting at 242–243°. The latter on treatment with silver oxide and methyl iodide afforded a methiodide, $C_{10}H_{21}ON \cdot CH_3I$, melting at 232–233° (18, 30).

The above-described thermal degradations afford an insight into the molecule of cevine that centers about the nitrogen atom. The formation of the typical 2-ethyl-5-methylpyridine as well as its hexahydro derivative indicate that the nitrogen-containing moiety of cevine is closely related to the analogous portion of other *Solanum* and *Veratrum* alkaloids. Less easily interpretable is the formation of 1,2-benzohydrindane as well as the numerous fluorene derivatives. It is nevertheless not improbable that the carbon skeleton of cevine is similar to that of veratramine and of jervine.

OXIDATION WITH CHROMIC ACID. Extensive investigations of the products of the oxidation of cevine with chromic acid and sulfuric acid have been reported. Aside from two nitrogenous compounds, (a) C_5H_9ON , m.p. 58° and (b) $C_6H_{11}ON$, m.p. 34–37°, the main products are nitrogen-free acids. Among those of lower molecular weight there were obtained succinic and methylsuccinic acids as well as some regarded as higher homologs. The following of the higher-molecular-weight products were described:

- (a) Hexanetetracarboxylic acid, $C_{10}H_{14}O_8$, m.p. 170–175°.*
- (b) Heptanetetracarboxylic acid, $C_{11}H_{16}O_8$, m.p. 145–148°.
- (c) Lactonedicarboxylic acid, $C_{11}H_{14(16)}O_8$.
- (d) Lactonetricarboxylic acid, $C_{14}H_{18}O_8$.

All of these were isolated as their esters. Of special interest are the reactions of the hexanetetracarboxylic acid, which on heating first yields a dianhydride, $C_{10}H_{10}O_6$, and on further heating forms a ketonic anhydride, $C_9H_{10}O_4$.

The lactonetricarboxylic acid, $C_{14}H_{18}O_8$, on heating to 200° is converted into an acid, $C_{14}H_{14}O_6$, which has been named decevinic acid.

*The constitution 3-carboxy-4-carboxymethylheptan-1, 7-dioic acid was tentatively proposed for this acid by N. Elming, C. Vogel, O. Jeger and V. Prelog, *Helv. chim. acta*, **35**, 2541 (1952).

TABLE 13

REACTIONS OF DECEVINIC ACID

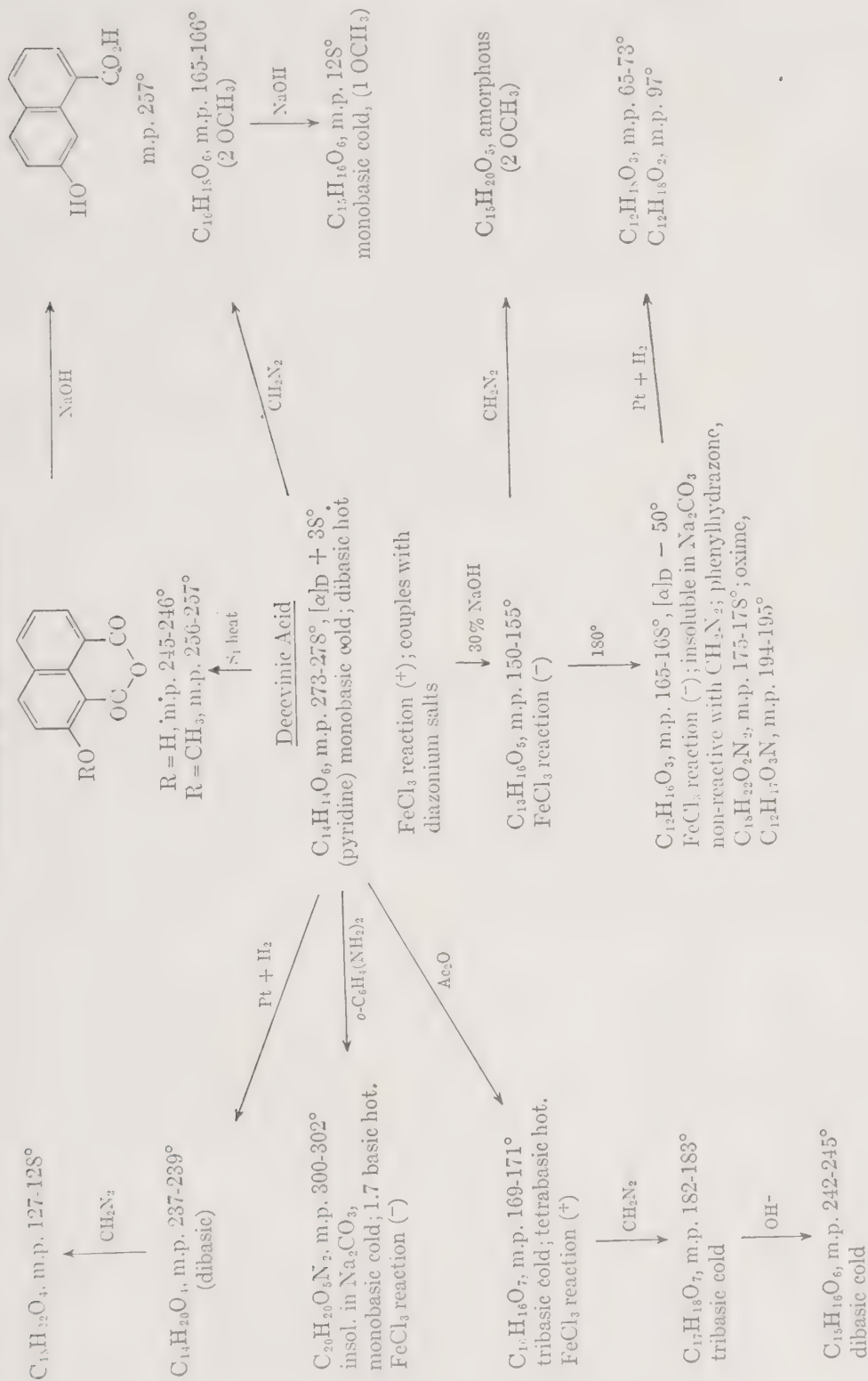


TABLE 14
PROPERTIES OF CEVINE AND ITS DERIVATIVES

Compound	Formula	M.p. °C.	$[\alpha]_D$	Ref.
Cevine (α -Cevine) ^a	$C_{27}H_{43}O_8N$	165–170 (sinters at 155)	–15.36° (CH_3OH), –17.52° (C_2H_5OH), –18.68° (50% C_2H_5OH), –30.8° (C_3H_5O)	16, 17, 30, 46
Hydrate	$C_{27}H_{43}O_8N \cdot 3\frac{1}{2}H_2O$	105–110		16, 17, 30, 46
Hydrochloride		240 (dec)		16, 17, 30, 46
Methiodide		240–250		16, 17, 30, 46
Methochloride ^b		280–283	–1.5° (H_2O)	16, 17, 30, 46
Cevine potassium	$C_{27}H_{42}O_8NK \cdot KOC_2H_5$	275–278, 272–274	–23.7° (C_2H_5OH)	16, 22, 43
Cevine <i>N</i> -oxide	$C_{27}H_{43}O_9N$	208–210		17, 60a
Hydrochloride		185 (dec), amorph.		17, 60a
Aurichloride		195–196		17
Dibenzoylcevine	$C_{41}H_{51}O_{10}N$	227 (dec)		17
Hydrochloride		ca. 262		17
Nitrate		170, amorph.		17
Acetate		193–195		17
Benzoate		175 (sinters at 160)		17
Di-(<i>o</i> -nitrobenzoyl)cevine	$C_{41}H_{49}O_{14}N_3$	288–290 (dec)	+37° (C_2H_5OH), +23.8° ($CHCl_3$)	46
Tetracetylcevine	$C_{33}H_{51}O_{12}N \cdot H_2O$			60a
Perchlorate		244–245		60a
β -Cevine ^c	$C_{27}H_{43}O_8N$	amorph.	–18° (C_2H_5OH)	43
Hydrochloride		244–247		43
Oxime	$C_{27}H_{44}O_8N_2$	amorph.		43
Oxime hydrochloride	$C_{27}H_{44}O_8N_2 \cdot HCl$	amorph.		43

TABLE 14 (Continued)

Compound	Formula	M.p. °C.	$[\alpha]_D$	Ref.
Des- <i>N</i> -methylecveine (Cevine betaine) ^d	$C_{23}H_{45}O_8N \cdot H_2O$	270-277 (dec)		18, 30
Bicarbonate				18, 30
Hydriodide		256 (dec)		18, 30
Hydrobromide		271-273 (dec)		18, 30
Hydrochloride		258-261		18, 30
Picrate				18, 30
Compound $C_{27}H_{45}O_8N$		Not sharp and partly at 223-227 and partly at 255-260	-15° (CH ₃ OH)	43
Compound $C_{27}H_{45}O_8N$			-8° (CH ₃ OH)	43
Compound $C_{27}H_{45(47)}O_8N$		263-265	-27° (CH ₃ OH)	43
Compound $C_{27}H_{43-45}O_7N$		263-264	-21° (CH ₃ OH)	43
		284-287		

^a pK' 9.67 (25°); IR-absorption spectrum shows no carbonyl bands in the region 1600-1700 cm.⁻¹.

^b The alkamine reduces hot ammonical silver nitrate and Fehling's solutions.

^c pK' 9.55 (26.5°); IR-absorption spectrum shows no carbonyl bands in the region 1600-1700 cm.⁻¹; λ_{max} , 275 m μ (log ϵ 2.5).

^d Des-*N*-methylecveine on treatment with hydrogen chloride in ethanol forms a compound, $C_{23}H_{46}O_8NCl \cdot C_2H_5OH$, m.p. 242° (ethanol), $[\alpha]_D - 28^\circ$ (water); reaction with hydrogen chloride in methanol forms the compound $C_{23}H_{46}O_8NCl \cdot CH_3OH$, m.p. 248-250° (methanol).

The many and in part obscure reactions of this acid are summarized in Table 13. It has not been possible to interpret these reactions to arrive at a satisfactory structure for decevinic acid. Since it is formed from the lactone, $C_{14}H_{18}O_8$, by a reaction or reactions that are also not understood the many experimental results are at present of no service in elucidating the structure of cevine (6, 7, 11).

g. Germine. This alkamine (also α -germine), $C_{27}H_{43}O_8N$, was first obtained by Poethke (51 cf. also 44a, 45, 49a) by alkaline hydrolysis of the ester germerine. Little is known of its structure, but the results of the limited investigations indicate a close analogy to the isomeric cevine (13).

Germine has a basic tertiary nitrogen and forms crystalline salts. It reacts with hydrogen peroxide to generate an *N*-oxide, which on reduction with sulfur dioxide regenerates germine (51).

Of the eight oxygens, five can be characterized as hydroxyls, since a pentacetyl derivative, $C_{27}H_{53}O_{13}N$, is obtained when germine is reacted with acetic anhydride-pyridine at room temperature. This compound on methanolysis at room temperature regenerates germine (27a). At least two of the hydroxyls are in the 1,2- or 1,3-position with respect to themselves since reaction of the alkamine with acetone and hydrogen chloride leads to the formation of the hydrochloride of acetonylgermine, $C_{30}H_{47}O_8N \cdot HCl$, from which the free base can be generated (19, 51).

Treatment of germine with dilute alkali isomerizes it to β -germine and isogermine, the latter having also been obtained from the mother liquors from the preparation of germine. In contradistinction to germine, which does not react with carbonyl reagents, both β -germine and isogermine form an oxime, $C_{27}H_{44}O_8N_2$, which is apparently the same from both sources. The isomerization is interpreted to indicate an α,β -unsaturated hydroxyl which first forms an enolate and then rearranges to a ketone. In conformity therewith, isogermine shows a strong band at ca. 1715 cm^{-1} in the IR-spectrum which is characteristic of six-membered cyclic ketones (14, 43).

Germine and isogermine behave quite differently on catalytic hydrogenation, only the latter reacting to form dihydroisogermine, $C_{27}H_{45}O_8N$. When germine is reduced with sodium and butanol an apparently isomeric dihydro derivative is formed (43).

The close structural relation of germine with cevine is indicated by the following compounds which were obtained from the selenium dihydrogenation products: β -picoline, 2-ethyl-5-methylpyridine, cevanthrol, and cevanthridine. Finally, germine on oxidation with chromic-sulfuric acid afforded the same hexanetetracarboxylic acid, $C_{10}H_{14}O_8$, that was similarly obtained from cevine (13).

h. Protoverine, $C_{27}H_{43}O_9N$, was first obtained by Poethke (51) by

TABLE 15
PROPERTIES OF GERMINE AND ITS DERIVATIVES

Compound	Formula	M.p. °C.	$[\alpha]_D$	Ref.
Germine (α -Germinine) ^a	C ₂₇ H ₄₃ O ₈ N	Crystallizes from methanol with 2 moles of the solvent, m.p. 220 after previous sintering at 163–173	+5° (C ₂ H ₅ OH)	13, 14, 19, 43, 51
Picronate		249 (dec)		
Pentaacetylgermine	C ₃₇ H ₅₃ O ₁₃ N	256–257 (dec)	–85° (C ₆ H ₅ N)	13, 14, 19, 43, 51
Tetrapropionylgermine	C ₃₅ H ₄₉ O ₁₂ N	216–217	–92.4° (C ₆ H ₅ N)	63
Triisobutyl derivative	C ₃₉ H ₆₁ O ₁₁ N	197–201	–65.8° (C ₆ H ₅ N)	63
Tetrabenzoylgermine	C ₅₅ H ₅₉ O ₁₂ N	223–225 (dec)	–16.8° (C ₂ H ₅ OH—CHCl ₃ , 1:1); –69° (C ₆ H ₅ N)	63
Pentahexahydrobenzoylgermine	C ₆₂ H ₉₃ O ₁₃ N	202–205	–60.4° (C ₆ H ₅ N)	63
β -Germinine ^b	C ₂₇ H ₄₃ O ₈ N	Crystallizes from methanol with 2 moles of the solvent, m.p. 169–171.5	+6° (C ₂ H ₅ OH)	43
Oxime	C ₂₇ H ₄₄ O ₈ N ₂	256–261.5	+16.4° (C ₂ H ₅ OH)	43
Isogerminine ^c	C ₂₇ H ₄₃ O ₈ N	245–260, 250–252	–46.5° (C ₂ H ₅ OH)	13, 43
Oxime	C ₂₇ H ₄₄ O ₈ N ₂	253–261.5	+18° (C ₂ H ₅ OH)	13, 43
Acetonylgermine ^d	C ₃₀ H ₄₇ O ₈ N	235–239		
Hydrochloride		255–275 (dec)		13
Dihydrogerminine ^e	C ₂₇ H ₄₅ O ₈ N	258–265	–57° (C ₆ H ₅ N)	14
Hydrochloride		250 (dec)		14
Dihydroisogerminine ^e	C ₂₇ H ₄₅ O ₈ N	277–278	–61° (C ₆ H ₅ N)	14

^a Does not form a sparingly soluble digtonide; anhydrous germine contains 8 active hydrogens.

^b λ_{\max} . ca. 280 m μ (log ϵ 2.2) (C₂H₅OH).

^c λ_{\max} . ca. 280 m μ (log ϵ 2.0) (C₂H₅OH); IR-absorption spectrum, band at 1715 cm.^{–1} (Nujol).

^d 6 active hydrogens.

^e 8 active hydrogens.

the alkaline hydrolysis of protoveratrine. Little is known regarding its structure, but it shows certain analogies to cevine and germine and a structural similarity with these is mooted (12, 43).

The basic nitrogen in protoverine is tertiary. Two of the nine oxygens are present as hydroxyls which lend themselves to condensation with acetone in the presence of hydrogen chloride. There is thus formed acetonylprotoverine, $C_{30}H_{47}O_9N$, which still shows seven active hydrogens by the method of Zerewitinoff. Protoverine can also be isomerized by the action of alkali to isoprotoverine, $C_{27}H_{43}O_9N$, which on hydrogenation in methanol with a platinum catalyst yields dihydroisoprotoverine. The latter compound is also obtained by the direct reduction of protoverine with sodium and butanol (34, 43).

TABLE 16
PROPERTIES OF PROTOVERINE AND ITS DERIVATIVES

Compound	Formula	M.p. °C.	$[\alpha]_D$	Ref.
Protoverine	$C_{27}H_{43}O_9N$	195–200	–12° (C_6H_5N)	51
Hydrate	$C_{27}H_{43}O_9N \cdot H_2O$	210–216		34
Picrate				51
Piconolate				51
Acetonylprotoverine	$C_{30}H_{47}O_9N$	253–256, sinters at 235		34
Hydrochloride		278–281		34
Isoprotoverine	$C_{27}H_{43}O_9N$	240–264, 254 (dec)	–42° (C_6H_5N)	34
Oxime	$C_{27}H_{44}O_9N_2$	237–248		34
Dihydroisoprotoverine	$C_{27}H_{45}O_9N$	315–320	–49° (C_6H_5N)	34
Dihydroprotoverine ^a	$C_{27}H_{45}O_9N$	330–335 (dec)	–54° (C_6H_5N)	34

^a Is presumably identical with dihydroisoprotoverine.

i. Zygadenine.

ISOLATION. This little-known alkaline has been obtained from *Zygadenus indermedius* Rydb. and *Z. venenosus*. The dried plant material was exhaustively extracted with ethanol by maceration, and the residue from the evaporated extract extracted with aqueous tartaric acid. The resultant aqueous solution was treated with sodium carbonate or with sodium hydroxide, and the liberated base mixture extracted with ether and with chloroform. The zygadenine crystallized when the bases were left in contact with ethanol.

Because of its empirical formula, $C_{27}H_{43}O_7N$, and because of its known reactions, zygadenine is possibly closely related to cevine and germine. It has a basic tertiary nitrogen, and six hydroxyls are shown to be present by the formation of a hexacetyl derivative (23, 24).

Zygadenine can be isomerized to pseudozygadenine by the action of

alkali, and this on treatment with acetic anhydride-pyridine is converted into a triacetyl derivative. Pseudozygadenine is also obtained by the alkaline hydrolysis of veratroyl- and vanilloylzygadenine, which have been isolated from *Z. venenosus* (45).

TABLE 17
PROPERTIES OF ZYGADENINE AND ITS DERIVATIVES

Compound	Formula	M.p. °C.	$[\alpha]_D$	Ref.
Zygadenine ^a	C ₂₇ H ₄₃ O ₇ N	200–201 or 201–204	–48°, –45° (CHCl ₃)	23, 24, 45
Aurichloride		140–165 (dec)		23, 24, 45
Acid sulfate		237–242 (dec)		23, 24, 45
Hydrochloride		231–234 (dec)		23, 24, 45
Hexacetylzygadenine	C ₃₉ H ₅₅ O ₁₃ N	265–270		24
Pseudozygadenine	C ₂₇ H ₄₃ O ₇ N	169–171 (dec)	–33° (CHCl ₃)	45
Triacetylpseudozygadenine	C ₃₃ H ₄₉ O ₁₀ N	253–256 (dec)	–33° (CHCl ₃)	45

^a Not precipitable with digitonin.

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CHAPTER 22

β -Phenethylamines

L. RETI

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	<i>Page</i>
I. Introduction.	313
II. Biosynthesis	315
III. Chemistry of the β -Phenethylamines Found in Plants	316
1. β -Phenethylamine	316
2. <i>N</i> -Methyl- β -phenethylamine.	317
3. Halostachine.	317
4. Tyramine.	318
5. <i>N</i> -Methyltyramine.	319
6. Hordenine.	320
7. Candicine.	321
8. <i>O</i> -Methyltyramine- <i>N</i> -methyleinnamide	322
9. 3-Hydroxytyramine.	322
10. Coryneine.	323
11. Mescaline.	324
<i>a.</i> Synthesis of Mescaline According to Kindler and Peschke.	326
<i>b.</i> Synthesis of Mescaline According to Slotta and Syszka.	326
12. <i>N</i> -Methylmescaline.	328
13. <i>N</i> -Acetylmescaline	328
14. Trichocereine	328
IV. Pharmacology of the β -Phenethylamines.	329
1. Sympathomimetic amines.	329
2. Halostachine.	330
3. Hordenine.	330
4. Candicine.	331
5. Coryneine.	331
6. Mescaline.	331
7. Trichocereine	334
V. References.	334

I. Introduction

After the determination of the structure of the adrenaline molecule (Friedmann, 1904) and the discovery of tyramine in putrified meat and ergot (1) much interest was aroused in compounds of similar chemical constitution. Shortly afterwards, Barger and Dale (2) examined pharmacologically a large series of amines, structurally related to adrenaline and tyramine.

The basic skeleton of the adrenaline molecule is that of a β -phenethylamine. In 1910, when Barger and coworkers made their first studies, only three naturally occurring compounds of this type were

known: adrenaline, tyramine, and hordenine. Since then several other β -phenethylamines have been identified as constituents of plants of widely separated botanical families. It is a remarkable coincidence that the majority of the newly-found natural phenethylamines had already been studied by Barger and Dale (phenethylamine, *N*-methylphenethylamine, *N*-methyltyramine, candicine, oxytyramine, coryneine, halostachine, noradrenaline).

Interest in natural and synthetic phenethylamines mounted when Späth in 1919 (3) recognized the β -phenethylamine skeleton in mescaline, the hallucinatory principle of the "peyote." Peyote has been recently discussed in newspapers and current magazines in connection with the campaign against narcotics. An interesting statement has been made by La Barre *et al.* (174) against the inclusion of peyote in the list of narcotics. It is partially transcribed as follows:

"In connection with the campaign against narcotics, there has been some propaganda to declare illegal the peyote used by many Indian tribes. The authors, professional anthropologists, protest against this campaign. Peyote is not a narcotic. It does not excite, stupefy, or produce muscular incoordination; there is no hangover; and the habitual user does not develop any increased tolerance or dependence. As for the immorality that is supposed to accompany its use, the charge is also completely invalid. Actually Peyotism is a religion, incorporated under the name of "The Native American Church of the United States." Its modern form, developed about 1870, is Christianity adapted to traditional Indian beliefs and practices . . . is a legitimate religious organization deserving of the same right to religious freedom as other Churches; also that peyote is used sacramentally in a manner corresponding to the bread and wine of white Christians."

There is little doubt that other β -phenethylamines will be found to be primary plant constituents and their structures can even be predicted based on the regularity with which the substituents appear to occur in the already known natural compounds. A "missing link" has been recently discovered by Kirkwood and Marion (4) in certain strains of barley. The newly found *N*-methyltyramine completes the series which begins with tyramine and terminates in the quaternary cactus alkaloid candicine.

It would appear as though the natural phenethylamines were connected with some general biochemical mechanism, which is not even limited to plants alone. Even adrenaline, this typical animal hormone may be expected to occur in plants; its chemical skeleton is already represented in halostachine (side chain) and in oxytyramine and coryneine (3:4 position of the hydroxyls). The occurrence of adrenaline (5%) in

the skin secretion of a number of tropical and subtropical toads may be mentioned (5).

II. Biosynthesis

There is a general agreement that the natural phenethylamines are biogenetically linked to the naturally occurring aromatic amino acids, such as phenylalanine, tyrosine, *N*-methyltyrosine and 3:4 dihydroxyphenylalanine (dopa). This derivation involves only very simple and biologically plausible reactions, such as decarboxylation, oxidation, and *O*- and *N*-methylation.

The biological formation of simple and more complex natural amines is thoroughly discussed in Guggenheim's fundamental treatise (6).

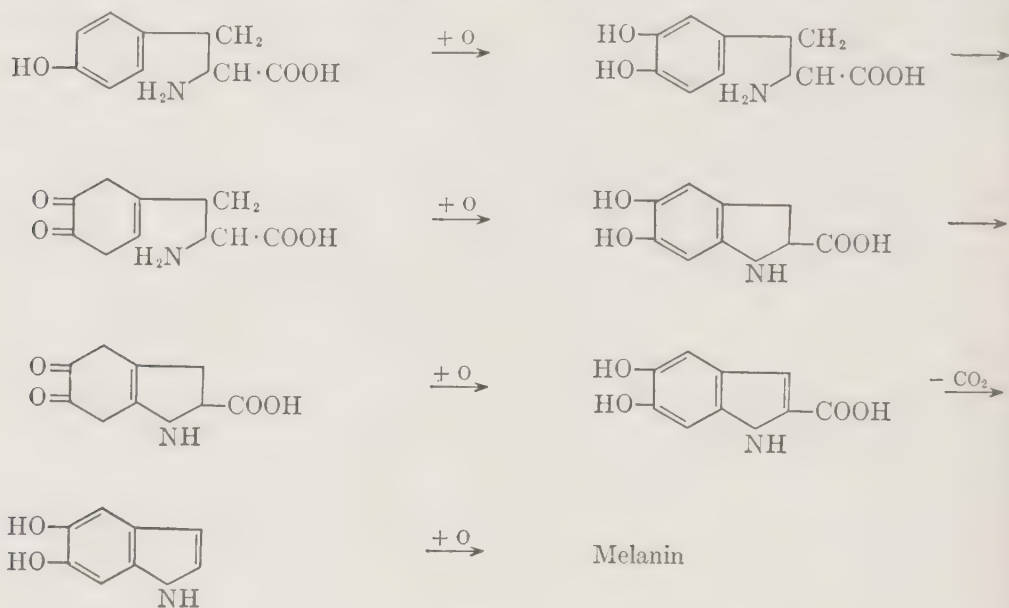
Naturally occurring β -phenethylamines may have been formed by biological decarboxylation of the protein amino acids, phenylalanine, and tyrosine. For the di- and trihydroxy derivatives the corresponding substituted phenylalanines should be considered, although 3:4-dihydroxyphenylalanine (dopa) does not seem to occur in proteins while the trihydroxy derivative has yet to be found in nature. However, it is not necessary to suppose that alkaloids are formed directly from the amino acids of proteins. Several workers, especially Guggenheim, suggest the possibility that both amino acids and alkaloids originate from common parent substances.

The biological oxidation of phenylalanine to tyrosine and its conversion to 3:4-dihydroxy derivatives is an established fact. The direct conversion of phenylalanine to tyrosine in the animal body has been demonstrated by Moss and Schoenheimer (7), by feeding phenylalanine with deuterium in the benzene ring. According to Bernheim and Bernheim (8), this conversion can be regarded as a step in normal intermediary metabolism and is probably dependent upon a specific enzyme system.

The oxidation of tyrosine, tyramine, or *N*-methyltyramine by tyrosinase has been the subject of extended studies. The reaction sequence follows the route outlined by Raper (9, 10) and Duli  re and Raper (11) as shown in the formula on page 316.

The biological conversion of phenylalanine into adrenaline in mammalian tissues (involving oxidation, decarboxylation, and methylation) is strongly supported by the work of Gurin and Delluva (12). *d,l*-Phenylalanine, labelled with ^{14}C in the carboxyl group and α -carbon, was converted to adrenaline in which the ^{14}C was located in the terminal carbon of the side chain. Similar results were obtained with tritium-labeled phenylalanine. The results suggest that this biological conversion not only involves decarboxylation of phenylalanine (or one of its derivatives) but that the aminoethyl side chain formed remains attached to the benzene nucleus during the biological synthesis.

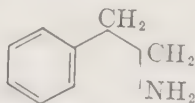
It may be assumed that the biosynthesis of β -phenethylamines in plant tissues follows a similar pattern. The general occurrence of decarboxylases, tyrosinases as well as melanization phenomena gives strong support to this hypothesis, although reliable experimental evidence, such as has been obtained in the case of animal metabolism, is not yet available



It is interesting that the tertiary and quaternary tyramine derivatives found in the cacti, such as hordenine and candicine, although they take up appreciable amounts of oxygen, do not form pigments when oxidized by tyrosinase [Dulière and Raper (11)]. However, tyrosine or some other derivative must be present in all cacti since the darkening of cut stems, preceded by a red phase, is characteristic for the whole family. Roca (13) found tyrosine, tyrosinase, and unidentified alkaloidal substances in the Mexican cactus, *Pachycereus marginatus* Britton and Rose. Tyrosinase has been observed also in *Trichocereus candicans* Britton and Rose, which contains the alkaloids candicine and hordenine.

III. Chemistry of the β -Phenethylamines Found in Plants

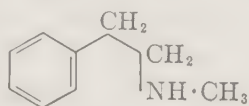
1. β -PHENETHYLAMINE, $C_8H_{11}N$



Phenethylamine, isolated in many instances from the putrefactive decomposition products of proteins (cf. Guggenheim (6)), occurs also as

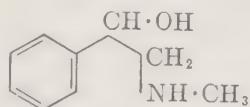
a primary plant constituent. The base found by Leprince (14) in mistletoe (*Viscum album* L.) was probably phenethylamine. White (15) isolated the compound from many species of acacia. It is a colorless strongly basic oil, $D^{24}_D = 0.9580$; b.p. 198° (760 mm); slightly soluble in water, readily soluble in alcohol and ether. The hydrochloride has m.p. 217° ; oxalate, m.p. 218° ; the platinichloride crystallizes in golden leaflets from alcohol containing hydrochloric acid; insoluble in water, m.p. $253\text{--}254^\circ$; aurichloride, m.p. $98\text{--}100^\circ$; pierate, m.p. $171\text{--}174^\circ$.

2. N-METHYL- β -PHENETHYLAMINE, $C_9H_{13}N$



N-Methyl- β -phenethylamine occurs together with dipterine (N-methyltryptamine) and leptocladine (3:4-dimethyl-3:4:5:6-tetrahydro-4-carboline), in the Chenopodiaceae *Arthrophytum leptocladum* Popov (16, 17). The colorless oil has b.p. $72\text{--}75^\circ$ (4 mm.); hydrochloride, m.p. $161\text{--}162^\circ$, pierate $141\text{--}142^\circ$ (from alcohol); pierolonate, m.p. $217\text{--}218^\circ$ (from alcohol); platinichloride, m.p. $220\text{--}221^\circ$; methiodide of the methyl compound, m.p. $227\text{--}228^\circ$.

3. HALOSTACHINE (PHENETHANOLMETHYLAMINE), $C_9H_{13}ON$



Halostachine was discovered by Yu. I. Syrneva (18) in the Chenopodiaceae *Halostachys caspica* C. A. Mey. The erroneously assigned molecular structure, $C_6H_5 \cdot CH(NH \cdot CH_3)CH_2OH$, was later corrected by G. P. Menshikov and M. N. Rubinstein (19) to $C_6H_5 \cdot CH(OH)CH_2NH \cdot CH_3$.

The plant contains, according to the mentioned authors, an optically inactive amino acid, $C_5H_{11}O_2N$, and the base halostachine, $C_9H_{13}ON$. The free base melts at $43\text{--}45^\circ$ and has $[\alpha]_D - 47.03^\circ$; the hydrochloride, m.p. $113\text{--}114^\circ$, has $[\alpha]_D - 52.21^\circ$; N-methylhalostachine has b.p. $125\text{--}127^\circ$ (20 mm.), $[\alpha]_D - 65^\circ$, it yields a methiodide, m.p. $230\text{--}231^\circ$ (from alcohol).

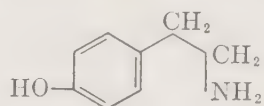
Halostachine is oxidized to benzoic acid by permanganate. It reacts with thionylchloride giving $C_6H_{12}NCl \cdot HCl$, m.p. $168\text{--}169^\circ$ (from alcohol); N-methylhalostachine yields with thionylchloride $C_{10}H_{14}NCl \cdot HCl$, m.p. $202\text{--}203^\circ$. This compound is reduced by sodium amalgam to the base $C_{10}H_{15}N$ (identical with N-dimethyl- β -phenethylamine), b.p.

203–205° (picrate, from alcohol, m.p. 133–134°). Halostachine has thus the structure $\text{C}_6\text{H}_5\cdot\text{CH}(\text{OH})\text{CH}_2\text{NH}\cdot\text{CH}_3$.

The racemic compound has been prepared synthetically and examined by Barger and Dale (2) and later by Hyde, Browning, and Adams (20).

G. P. Menshikov and G. M. Borodina (21) synthesized both optical isomers of methylaminophenethanol and showed the identity of the *l*-form with natural halostachine. The compound, $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CH}_2\text{N}\cdot\text{CH}_3(\text{CH}_2\cdot\text{C}_6\text{H}_5)$ was reduced with hydrogen and palladium chloride, and after treatment with sodium hydroxide solution, inactive $\text{C}_6\text{H}_5\text{CH}(\text{OH})\cdot\text{CH}_2\text{NH}\cdot\text{CH}_3$ was obtained. The racemate, m.p. 75–76° (from ether-petrol ether) was resolved with *d*- and *l*-tartaric acid to the optical antipodes. The *d*-tartrate of the *l*-base had m.p. 112–115° and $[\alpha]_D - 18.73^\circ$; the *l*-tartrate of the *d*-base also melted at 112–115°; $[\alpha]_D + 18.62^\circ$. The free bases were recovered by treatment of the tartrates with 20% sodium hydroxide and isolated as hydrochlorides; m.p. of both hydrochlorides, 113–114°; *l*-form $[\alpha]_D - 52.46^\circ$; *d*-form $[\alpha]_D + 52.78^\circ$. Mixed melting points of the derivatives of natural halostachine with the *l*-derivatives of the synthetic base showed their identity.

4. TYRAMINE (*p*-HYDROXY- β -PHENETHYLAMINE), $\text{C}_8\text{H}_{11}\text{ON}$



Tyramine, as a degradation product of tyrosine, appears in several metabolic and fermentation processes involving proteins. Observations of this nature are surveyed in Guggenheim's book (6). However, tyramine occurs also as an unquestionable primary constituent in plants and animals. Barger (1, 22), found small quantities of tyramine in ergot, where it is accompanied by a considerable number of other bases (see also Freudweiler (23); Funck and Finck (24). It occurs together with tyrosine in the salivary or venom glands of cephalopods (Henze (25, 26; Bottazzi (27)). Crawford and Watanabe (28, 29) found the base in several species of American mistletoes (*Phoradendron flavescens* Nutt., *Ph. villosum* Nutt., *Ph. californicum* Nutt.). The European mistletoe, *Viscum album* L., also contains tyramine, according to Ostemberg (30). Ullmann (31) found tyramine in the thistle, *Silybum marianum* Gaertn. According to Schmalfuss and Heider (32) the common broom, *Cytisus scoparius* Link. (*Sarothamnus scoparius* Koch.), contains tyramine and 3:4-dihydroxyphenethylamine.

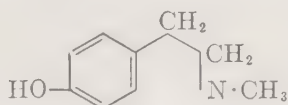
Tyramine crystallizes from alcohol in white, hexagonal leaflets, m.p.

161°; b.p. 175–178° (8 mm.); one part is soluble at 15° in 95 parts of water and in 10 parts of hot alcohol. It is slightly soluble in amyl alcohol and much less so in ether or chloroform. The salts crystallize well: the hydrochloride, from conc. hydrochloric acid, is very soluble in water, m.p. 268–269°; picrate, m.p. 206°; dibenzoate, m.p. 174°; oxalate, m.p. 203–204°. The dicarbomethoxy derivative melts at 100.5°.

Tyramine, like other *p*-hydroxy compounds, gives a positive Millon reaction.

Barger (22) synthesized the base by reduction of *p*-hydroxyphenylacetonitrile with sodium. Barger and Walpole (33) later described two other syntheses. The *p*-hydroxy group was introduced into phenylethylamine by nitration, reduction, diazotization etc., or anisaldehyde was converted to *p*-methoxyphenylpropionamide, from which, by Hofmann degradation and demethylation, tyramine was obtained. Rosenmund (34) condensed anisaldehyde with nitromethane, and obtained tyramine by reduction followed by demethylation. Further syntheses of tyramine have been described by Kondo and Shinozaki (35), Slotta and Altner (36), Koessler and Hanke (37), Kindler and Peschke (38) and Buck (39, 40). A well known method of preparation is the thermal decarboxylation of tyrosine. Waser (41) obtained a 96% yield by heating the amino acid suspended in a high boiling solvent (fluorene).

5. *N*-METHYLTYRAMINE (β -*p*-HYDROXYPHENETHYLMETHYLAMINE)

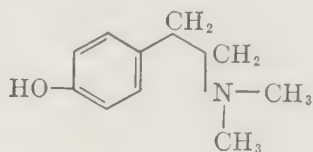


N-Methyltyramine was recently discovered by Kirkwood and Marion (4) in certain strains of barley. All attempts to isolate hordenine from these strains, which were regarded as spontaneous mutants, failed and it is presumed that they produce only *N*-methyltyramine. The base has long been known as a product of the thermal or putrefactive decarboxylation of the natural *N*-methyltyrosine, having been described at various times as surinamine, angeline, andirine, geoffroyine, and rhatanine (42–47).

The free base is only slightly soluble in water. It crystallizes well from alcohol in prisms, from benzol in leaflets, from anisole in stubby needles, m.p. 130–131°; hydrochloride, m.p. 148.5°; platinichloride, m.p. 205–206°; picrate, m.p. 149°; picrolonate, m.p. 234–235°; *N*-acetyl-*N*-methyltyramine, from *N*-methyltyramine and acetic anhydride, m.p. 143°; *O*-methylether hydrochloride, m.p. 181–182°, picrate, m.p. 112° (47a). A synthesis of *N*-methyltyramine was described by Walpole (43).

Corti (48) prepared the base by heating *N*-methyltyrosine, suspended in fluorene, at 250°. Kirkwood and Marion (4) condensed *O*-methyltyramine with benzaldehyde and treated the derived benzal derivative with dimethyl sulfate. After decomposition of the quaternary compound and hydrolysis of the *O*-methyl-*N*-methyltyramine with hydrobromic acid *N*-methyltyramine was obtained.

6. HORDENINE (ANHALINE, β -*p*-HYDROXYPHENETHYLDIMETHYLAMINE),
C₁₀H₁₅ON



This compound was found first in the cactacea *Anhalonium fissuratum* Engelm. (*Mammillaria fissurata* Engelm.) by Heffter (49) in 1894 and named anhaline. In 1906 Leger (50–58) isolated from barley malt germs a base that he called hordenine—a discovery made by Gaebel (59) almost simultaneously. Subsequently, it was shown by Späth (3) that anhaline is identical with hordenine. Hordenine occurs also in the seedlings of other cereals: barley, *Hordeum sativum* Pers. (*H. vulgare* L.) contains 0.17%, *Panicum miliaceum* L. 0.24% and *Sorghum vulgare* Pers. (*Andropogon sorghum* Brot.) 0.07 (Hashitani, 60, 61). Reti (62) found hordenine and candicine, the corresponding quaternary ammonium-base, in the cacti *Trichocereus candicans* and *Trichocereus lamprochlorus* Britton and Rose (63). The former may be considered the richest natural source of hordenine (0.5–5%); *Anhalonium fissuratum* contains only 0.014% hordenine (Heffter, 49). Torquati (64), Reilhes (65) and Raoul (66–75) have studied the formation of hordenine during the germination of barley. Unsprouted seeds contain no hordenine; the alkaloid content reaches a peak (0.45%) 4 days after germination and disappears again about a month later. Raoul (67, 69, 72, 73) attempted to demonstrate that hordenine is formed in the barley by decarboxylation of tyrosine and methylation of the resulting tyramine by formaldehyde.

Methods of estimation have been described by Janot and Faudemay (76), Hashitani (61), Arnolt (77), Raoul (71), Gonnard (78) and Pedinelli (79).

In the absence of other *p*-hydroxy compounds the color reaction with Millon's reagent can be used quite satisfactorily for qualitative and quantitative estimations.

Hordenine may be obtained, starting from sprouted barley, as follows:

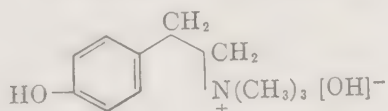
Dry seedlings are extracted with 95 % ethyl alcohol and the extract concentrated to dryness. The residue is taken up in dilute sulfuric acid and the filtered solution extracted with ether. The aqueous layer is made alkaline with sodium carbonate and extracted with ether. The ether extract is dried over sodium sulfate and allowed to evaporate until hordenine crystallizes. The base may be purified by distillation under reduced pressure or by recrystallization from alcohol or ether.

Hordenine crystallizes well in colorless prisms, m.p. 117–118°; b.p. 173–174° (11 mm.); it sublimes at 140–150°; is readily soluble in water, alcohol, ether, and chloroform. It is strongly alkaline and liberates ammonia from its salts; hydrochloride, m.p. 176.5–177.5°; sulfate, m.p. 209–211°; picrate, m.p. 139–140°; picrolonate, m.p. 219–220°; methiodide, m.p. 233–234° (Kirkwood and Marion, 4); acetylhordenine hydriodide, m.p. 176–177°; reineckate, m.p. 176–178° (78); benzoylhordenine, m.p. 47–48°.

Léger (56) showed that *O*-methyl-hordenine methiodide yields *p*-vinylanisole and trimethylamine on treatment with alkali and *O*-acetyl-hordenine is oxidized by permanganate to *p*-acetoxybenzoic acid. Hordenine is therefore β -*p*-hydroxyphenethyltrimethylamine, a structure confirmed by several syntheses.

Barger (80) starting from phenethyl alcohol, obtained phenethyl chloride, which, when heated with dimethylamine, yielded dimethylphenethylamine. By nitration, reduction, diazotization, etc. a base identical with natural hordenine was obtained. Rosenmund (81) condensed *p*-methoxybenzaldehyde with nitromethane and reduced the alkoxy nitrostyrene to *p*-methoxyphenethylamine. With methyl iodide a mixture of bases was formed from which, after demethylation with boiling hydroiodic acid, hordenine was obtained in low yield. Voswinkel (82) treated *p*-methoxyphenacyl chloride with dimethylamine, then demethylated and reduced to hordenine. Ehrlich and Pistschimuka (83) started from tyrosol, $p\text{-OH}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\text{CH}_2\text{OH}$, converted it to the chloride, which, with dimethylamine gave hordenine. Further synthesis have been elaborated by Späth and Sobel (84) and by Kindler (38). Raoul (67, 69) obtained hordenine in 50 % yield, by methylating tyramine with formaldehyde and formic acid.

7. CANDICINE (β -*p*-HYDROXYPHENETHYLTRIMETHYLAMMONIUM HYDROXIDE), $\text{C}_{11}\text{H}_{19}\text{O}_2\text{N}$



The quaternary ammonium base candicine was found by Reti (62) in the Argentine cactus *Trichocereus candicans*, in *T. lamprochlorus*

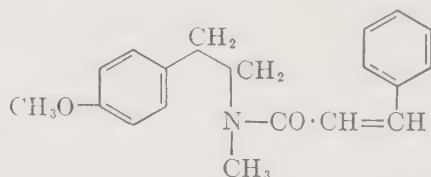
0.3 – 0.5% (Reti and Arnolt, 63), and in *T. spachianus* Riccob. (85). *T. candicans* may contain as much as 5% candicine, together with variable amounts of hordenine.

Candicine, like other quaternary compounds, cannot be extracted from alkaline solution with immiscible solvents. It was isolated by precipitating the purified plant extract with concentrated Mayer's reagent and then decomposing the precipitated mercuriodide with hydrogen sulfide, the base being recovered in the form of its slightly soluble iodide.

It forms well-crystallized salts (Castrillón, 86). The iodide (hordenine methiodide) has m.p. 234°; chloride, very hygroscopic, m.p. 285° (dec); platinichloride, m.p. 208–209°; aurichloride, m.p. 127–128; picrate, m.p. 162–163°; picrolonate, m.p. 218–219°; mercuriodide, m.p. 190–191°.

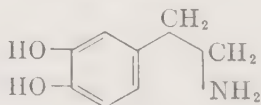
Candicine gives a red color reaction with Millon's reagent. The free base, obtained by heating a solution of the iodide with silver hydroxide, can be crystallized. Upon heating with alkali, it yields trimethylamine. *O*-Methylcandicine, under the same conditions is transformed into trimethylamine and *p*-vinylanisole. Anisic acid is obtained if *O*-methylcandicine is oxidized with permanganate.

8. *O*-METHYLTYRAMINE-*N*-METHYLCINNAMIDE [*N*-(2-*p*-ANISYLETHYL)-*N*-METHYLCINNAMIDE], $C_{19}H_{21}O_2N$



La Forge and Barthel (87) isolated this compound, which melts at 76°, from the bark of the southern prickly ash, *Zanthoxylum americanum* Mill (*Z. Clava-Herculis* Lam.), where it occurs together with berberine and asarinin. It has been obtained synthetically by the same authors, by reacting *O,N*-dimethyltyramine with cinnamoyl chloride.

9. 3-HYDROXYTYRAMINE (β -3:4-DIHYDROXYPHENETHYLAMINE), $C_8H_{11}O_2N$



Schmalfuss and Heider (32) identified the blood pressure-raising substances contained in the pod of the common broom, *Cytisus scoparius*, as tyramine and hydroxytyramine. Both may be considered as melanin

precursors. The amines were isolated with the aid of their carbomethoxy derivatives. The roots of *Hermidium alipes* S. Wats. (Nyctaginaceae) also contain hydroxytyramine, according to Buelow and Gisvold (88).

It gives the Millon test, reduces cold ammoniacal silver nitrate solution and shows characteristic color reactions with ferric chloride followed by alkalies. The following salts are known: hydrochloride, needles, very soluble in water, m.p. 241°; hydrobromide, m.p. 212°; tricarbomethoxy derivative, m.p. 92–93°; tribenzoyl derivative, m.p. 141°; picrate, m.p. 189°; styphnate, m.p. 206°.

The base can be obtained by heating 3:4-dihydroxyphenylalanine above its melting point. A synthesis starting from tyramine was described by Waser and Sommer (89): it was first nitrated to 3-nitrotyramine, reduced, and the diazo compound decomposed to 3-hydroxytyramine.

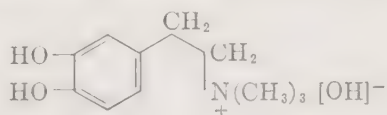
According to Holz and Credner (90) tyramine, in aqueous solution, when irradiated with ultraviolet light in the presence of air, is partly converted into 3-hydroxytyramine. The same substance results when oxygen is bubbled through a solution of tyramine and ascorbic acid. In both cases hydrogen peroxide seems to be an intermediate product.

Werle and Raub (91) observed that the seedlings of *Cytisus scoparius* are able to decarboxylate 3:4-dihydroxyphenylalanine to 3-hydroxytyramine, and Vinet (92) showed that kidney tissue, *in vitro*, can effect the same decarboxylation. Adrenal medulla converts the latter to adrenaline by methylation and oxidation, but cannot form adrenaline from dihydroxyphenylalanine or tyramine.

Some simple isoquinoline alkaloids (carnegine, salsoline, corypalline, hydrohydrastinine) may be considered as bio-products of the interaction of hydroxytyramine and acetaldehyde or formaldehyde, followed by methylation. Actually, Schöpf and Bayerle (93) obtained a surprisingly high yield of norcarnegine by carrying out this condensation under mild ("physiological") conditions, that is, at pH 5 and 25°.

The hydroxytyramine nucleus is chiefly involved in melanin formation (8, 9, 10, 11).

10. CORYNEINE (3-HYDROXYCANDICINE, β -3:4-DIHYDROXYPHENETHYL-TRIMETHYLAMMONIUM HYDROXIDE), $C_{11}H_{19}O_3N$



This quaternary base was isolated by Reti, Arnolt, and Ludueña (94) from *Stetsonia coryne* (Salm-Dyck) Britton and Rose, one of the

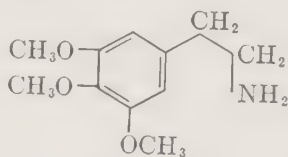
most striking tree-like cacti, which often forms the dominant feature of the landscape on the high plains of northern Argentina.

The base was extracted following the method used for isolating candicine. Special precautions had to be taken to avoid degradation of this sensitive catechol compound. The dry plant contains approximately 1% of this alkaloid.

Coryneine forms a crystalline chloride, $C_{11}H_{18}O_2NCl$, m.p. 201° . Three *N*-methyl groups are present in the molecule but *O*-methyl is absent. By *O*-methylation and subsequent permanganate, oxidation veratric acid is formed. Coryneine salts give the characteristic color reactions of catechol derivatives (ferric chloride and alkalies).

Barger and Ewins (95) prepared synthetic β -3:4 dihydroxyphenethyltrimethylammonium chloride and Barger and Dale (2) studied its pharmacological action. The two cactus alkaloids, coryneine and candicine, are interesting examples of substances found in nature long after they had been synthesized in the laboratory.

11. Mescaline (β -3:4:5-TRIMETHOXYPHENETHYLAMINE), $C_{11}H_{17}O_3N$



Mescaline, the active hallucinatory principle of the "mescal buttons" or "pellote," was isolated by Heffter (96) in 1896. Pellote (*Anhalonium lewinii* Hennings) contains up to 6% mescaline. Reti (97, 98) observed the presence of mescaline in the Argentine cactus *Trichocereus terscheckii*, Britton and Rose, which contains 0.2% trichocereine (dimethylmescaline) and 0.05% mescaline. Herrero-Ducloux (99) has assumed that one of the bases extracted from *Echinocactus gibbosus* D.C., (*Gymnocalycium gibbosum* Pfeiff.) was mescaline.

Microchemical reactions of mescaline have been described by Rosenthaler (100), Herrero-Ducloux (101), and Bolland (102).

The free base is a colorless strongly alkaline oil or crystals having m.p. $35-36^\circ$ (Kindler and Peschke, 103), b.p. 180° (12 mm.). It is soluble in water, alcohol, and chloroform, but only slightly so in ether. It readily absorbs carbon dioxide from the air forming the solid carbonate. The sulfate $(C_{11}H_{17}O_3N)_2 \cdot H_2SO_4 \cdot 2H_2O$ is particularly suited for isolation since it is insoluble in alcohol, only slightly soluble in cold water but very soluble in hot water; it forms brilliant prisms, m.p. $183-186^\circ$. The hydrochloride forms colorless crystals, m.p. 184° ; picrate, m.p. 222° ; the

aurichloride crystallizes with 1 H₂O, orange needles, m.p. 140–141°; platinichloride, straw-yellow needles, m.p. 187–188°; benzoyl derivative, m.p. 123°; *m*-nitrobenzoyl derivative, m.p. 161–162°; dimethylmescaline methiodide, m.p. 226–228°.

Heffter (104, 105, 106) determined the empirical formula of mescaline and found that upon oxidation the base yields trimethylgallic acid. Unfortunately, mescaline behaves in methylimino determinations as though it contained an *N*-methyl group. Heffter (107) synthesized 3:4:5-trimethoxybenzylmethylamine and found that it was not identical but isomeric with mescaline.

The irregularity mentioned was confirmed by Späth (3) who, guided by biogenetical considerations, arrived at the correct structure, in spite of the confusing analytical evidence. In Späth's mescaline synthesis 3:4:5-trimethoxybenzoyl chloride was reduced by the Rosenmund method (108) to the corresponding aldehyde, which when condensed with nitromethane yielded ω -nitro-3:4:5-trimethoxystyrene. This was reduced with zinc dust and acetic acid to the corresponding oxime and the latter was further reduced, by sodium amalgam, to β -3:4:5-trimethoxyphenethylamine, i.e., mescaline. Subsequently a number of improved syntheses have been reported.

Slotta and Heller (109, 110) prepared their starting material, viz., trimethoxyphenylpropionic acid by condensation of the substituted benzaldehyde with malonic acid and reduction of the resulting cinnamic acid. Mescaline was then obtained by Hofmann degradation of the trimethoxyphenylpropionamide. Kindler and Peschke (103) synthesized very pure, crystallized mescaline by condensation of 3:4:5-trimethoxybenzaldehyde with potassium cyanide, acetylation, and catalytic reduction to the amine. Slotta and Szyska (111, 112) improved Späth's first synthesis, obtaining mescaline directly by the electrolytic reduction of ω -nitrotrimethoxystyrene. Hahn and Wassmuth (113, 114) started from elemicine and first prepared trimethoxyphenylacetaldehyde by ozonization. The oxime was then reduced to mescaline. Kindler (115) and Kindler and Peschke (38, 103) improved the catalytic reduction of ω -nitrostyrenes to the corresponding phenethylamines. Hahn and Rumpf (116) described the preparation of mescaline by reduction of ω -nitrotrimethoxystyrene with Adam's catalyst. A review has been published by Jensch (117).

Several isomers of mescaline as well as mescaline-like compounds have been synthesized by Jansen (118–120); Slotta and Heller (110); Slotta and Szyska (111, 112); Slotta and Müller (121); Grace (122); Iwamoto and Hartung (123), and Hey (124). None of these compounds cause the euphoric state produced by mescaline.

a. *Synthesis of Mescaline According to Kindler and Peschke (103)*

i. *3:4:5-Trimethoxyacetylmandelonitrile.* Twenty grams 3:4:5-trimethoxybenzaldehyde, prepared according to Slotta and Heller (110), is mixed with 40 cc. of saturated sodium bisulfite solution. The separated bisulfite compound in a slurry with water is treated with a solution of 9.5 g. of potassium cyanide in 20 cc. water. The resulting nitrile is filtered, washed first with bisulfite solution then with water, and finally dried on a porous plate.

The mandelonitrile is acetylated by boiling for 1 hour with 100 cc. of acetic anhydride. The excess anhydride is distilled, the residue is dissolved in ether, and the solution washed successively with sodium carbonate solution, with bisulfite solution, and with water. The residue from the dried ether solution distills at 163–165° (0.1 mm.); yield, 82 % based on the 3:4:5-trimethoxybenzaldehyde.

ii. *Mescaline.* Twenty-two grams of 3:4:5-trimethoxyacetylmandelonitrile is dissolved in 200 cc. glacial acetic acid and the solution dropped into a suspension of 3 g. palladium black in 75 cc. acetic acid and 5 cc. concentrated sulfuric acid (for apparatus see *Arch. Pharm.* **1931**, 74). The introduction is made with agitation, at 18°, and under a hydrogen pressure of 2 atm. In 2½ hours, 95 % of the calculated amount of hydrogen is absorbed. An amount of potassium carbonate equivalent to the sulfuric acid is added, the acetic acid is eliminated *in vacuo*, and the residue dissolved in water. The aqueous solution is washed twice with ether, treated with excess potassium hydroxide, and the separated mescaline taken up in ether. The residue from the ether extract distills at 173° (10 mm.) and solidifies to white crystals, m.p. 35–36°.

b. *Synthesis of Mescaline, According to Slotta and Syszka (111)*

i. *3:4:5-Trimethoxybenzoyl Chloride.* Five hundred grams of 3:4:5-trimethoxybenzoic acid (cf. Gilman-Blatt, "Organic Syntheses," John Wiley & Sons, New York 1941, Collective Volume I, 537) is added to 285 cc. of thionyl chloride freshly distilled over linseed oil and the mixture is heated for 2 hours on a water bath. The still-hot mixture is then distilled under reduced pressure from a Claisen-flask, avoiding rubber stoppers. There is obtained 510 g. (93 % of theory) of trimethoxybenzoyl chloride boiling at 185° (18 mm.).

ii. *3:4:5-Trimethoxybenzaldehyde.* To a solution of 200 g. of 3:4:5-trimethoxybenzoyl chloride in 1000 cc. of xylene freshly distilled over sodium, there is added 60 g. of a 5 % palladium-barium sulfate catalyst. The mixture is heated in an oil bath maintained at 150° and a vigorous stream of hydrogen is introduced into the boiling solution. The hydrogen should be washed with aqueous permanganate and then dried with sulfuric acid. After 60–80 hours the reaction is complete. The solution is filtered and the aldehyde conveniently isolated as its bisulfite compound. Yield 120 g. (70.6 % of theory), m.p. 74°.

iii. *3:4:5-Trimethoxy- ω -nitrostyrene.* A solution of 40 cc. of nitromethane and 100 g. of trimethoxybenzaldehyde in 200 cc. alcohol is cooled to 0° and while it is stirred mechanically there is introduced a solution of 45 g. pure potassium hydroxide in 45 cc. water and 90 cc. methanol at the rate of about one drop per second, care being taken that the temperature does not rise. Fifteen minutes after the addition is completed the solution is poured into 500 cc. concentrated hydrochloric acid mixed with sufficient ice to assure its presence throughout the slow addition and to maintain a temperature of –10°. The precipitated nitrostyrene is separated by filtration and washing and may be purified by recrystallizing from 700 cc. alcohol. The pale

yellow plates which melt at 120–121° are obtained in a yield of approximately 78 % of theory.

iv. Mescaline. (A) APPARATUS (Fig. 1). A cell of porous porcelain (PC) (external dimensions: 75 \times 160) with a glazed rim is placed in a glass jar of 500 cc. capacity

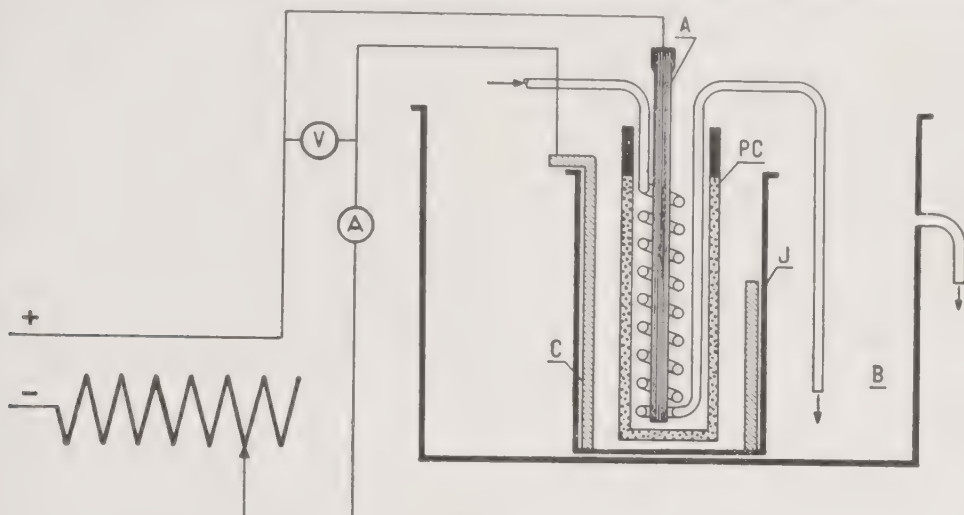


FIG. 1

(J), surrounded by a cooling bath (B). The anode (A) is a lead or carbon rod, surrounded by a glass coil; the cooling water flows through the coil and discharges into the cooling bath. The cathode (C) is a sheet of lead (220 \times 90 \times 2 mm.), which previous to each experiment is electrolytically coated with lead peroxide, in a bath of dilute sulfuric acid.

(B) REDUCTION. The cathode liquor consists of a solution of 30 g. 3:4:5-trimethoxy- ω -nitrostyrene in 100 cc. glacial acetic acid and 100 cc. alcohol, to which 50 cc. conc. hydrochloric acid has been added. The anodic compartment is filled, to the same level occupied by the catholyte, with a solution of 25 cc. conc. sulfuric acid in 175 cc. water.

The reduction requires 12 hours, using a current of 5–6 amperes; the cathode current density should be about 3 amperes per square centimeter. The temperature is regulated by the flow of the cooling water and the catholyte should be kept at 20° for the first six hours; the temperature is then allowed to rise until it reaches 40° at the end of the reduction.

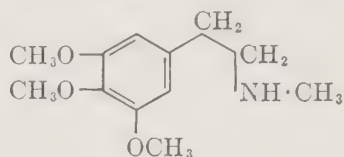
When the reduction is complete, the catholyte is filtered, evaporated in vacuum and the residue taken up in 300 cc. water. Unreduced nitrostyrene is extracted successively with ethyl acetate and with ether. The crude mescaline hydrochloride solution in a separatory funnel is then treated with a cold concentrated solution of 100 g. of sodium hydroxide and the liberated base exhaustively extracted with ether. The somewhat concentrated and dried (potassium carbonate) solution is treated with a stream of dry hydrogen chloride and the separated hydrochloride twice recrystallized from absolute alcohol. The pure mescaline hydrochloride thus obtained in 77 % yield forms white leaflets melting at 184°.

An improved synthesis of mescaline has been described by Benington and Morin (175). 3,4,5-Trimethoxy- β -nitrostyrene (176) was reduced

with lithium aluminum hydride, using a method described by Ramirez and Burger (177). The yield was of 86%.

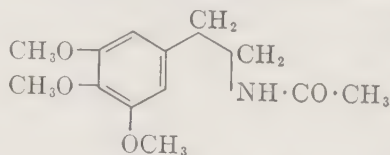
A new synthesis of mescaline has been recently elaborated by Tsao (178). The synthesis is outlined as follows: gallic acid \rightarrow 3,4,5-trimethoxybenzoic acid \rightarrow methyl ester of the 3,4,5-trimethoxybenzoic acid \rightarrow 3,4,5-trimethoxybenzyl alcohol \rightarrow 3,4,5-trimethoxybenzyl chloride \rightarrow 3,4,5-trimethoxyphenylacetonitrile \rightarrow mescaline. The reduction of the methyl ester and of the nitrile has been achieved using lithium aluminum hydride.

12. *N*-METHYLMESCALINE, $C_{12}H_{19}O_3N$



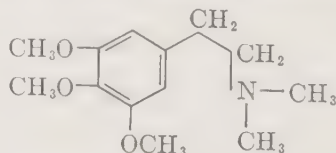
N-Methylmescaline was isolated by Späth and Bruck (125) from the mother liquors from the crystallization of the nonphenolic bases of "mescal-buttons." The identity of this base was established by comparison with synthetic *N*-methylmescaline which was obtained by the condensation of mescaline with benzaldehyde, followed by methylation of the benzal derivative with methyl iodide, and hydrolysis of the quaternary base; picrate, m.p. 177.5–178°; trinitro-*m*-cresolate, m.p. 189.5–190.5; *p*-nitrobenzoyl derivative, m.p. 142–143°.

13. *N*-ACETYLMESCALINE, $C_{13}H_{19}O_3N$



Späth and Bruck (126) detected *N*-acetylmescaline in "mescal buttons"; m.p. 93–94°. It is identical with *N*-acetylmescaline prepared by heating mescaline with acetic acid at 170–175°.

14. TRICHOCEREINE (*N,N*-DIMETHYLMESCALINE), $C_{13}H_{21}O_3N$



Trichocereine, together with mescaline, was found by Reti (97) in the Argentine giant cactus *Trichocereus terscheckii*. A further study and

the synthesis of the alkaloid was achieved by Reti and Castrillón (98). The dried plant contains 0.25 to 1.2% alkaloids. The ratio of trichocereine to mescaline was found to be 5:1, but in some lots, with high alkaloidal content, no mescaline could be detected. This is the first case where mescaline, the active principle of the "mescal buttons" (*Anhalonium lewinii*), has been found in a second species.

Trichocereine can be separated from mescaline by extraction with ether, in which the latter is only slightly soluble.

Trichocereine is a colorless basic oil; it distils *in vacuo* without decomposition and is soluble in water, alcohol, ether, and chloroform. The salts crystallize well; hydrochloride (from alcohol), m.p. 205°; picrate (from acetone), yellow needles, m.p. 171–172°; picrolonate (from alcohol-acetone), yellow prisms, m.p. 166°. If the melted salt is heated again, it melts at 175°. The platinichloride crystallizes from water and melts at 184–185°; aurichloride, m.p. 136–139 (with decomp.); methiodide, m.p. 226–228°; picrate of the quaternary *N*-methyl trichocereine (from water), m.p. 165°.

Trichocereine contains three methoxyl and two *N*-methyl groups. Upon oxidation with permanganate trimethylgallic acid is obtained. Trichocereine methiodide is identical with the methiodide obtained by exhaustive methylation of mescaline and trichocereine is therefore *N*-dimethylmescaline.

The alkaloid has been synthesized by reacting β -3:4:5-trimethoxyphenethylchloride with dimethylamine.

IV. Pharmacology of the β -Phenethylamines

1. SYMPATHOMIMETIC AMINES

The elucidation of the structure of adrenaline was the stimulus that started Barger and Dale on their classical studies, published in 1910 (2). They examined the adrenaline-like effect of a large number of compounds, and they found, on the whole, that approximation to adrenaline in the chemical structure is linked with an increase and a sharper specificity of the action. Barger and Dale introduced the term "sympathomimetic," which means that the effects produced resemble those obtained by stimulation of the so-called sympathetic system of nerves. The study of the sympathomimetic amines represents one of the earliest and most successful attempts to correlate pharmacological action with chemical structure. The sympathomimetic action includes rise of arterial blood pressure, stimulation of the heart muscle, constriction of the arterioles and either stimulation or inhibition of smooth muscle. Some of the drugs also stimulate the central nervous system.

The literature on sympathomimetic compounds is extensive and only some of the several excellent surveys such as Guggenheim's book (6), Beyer (127) and the 1945 Symposium in Industrial and Engineering Chemistry (128) can be mentioned.

According to Barger and Dale, the relative effects of some β -phenethylamines on blood pressure in decerebrated cats (isoamylamine = 1) are:

β -Phenethylamine	2-3
β -Phenethylmethylamine	2-3
Phenethanolmethylamine (racemic halostachine)	2-3
Tyramine	10
<i>N</i> -Methyltyramine	10
Hydroxytyramine	20
<i>N</i> -Methylhydroxytyramine (Epinine)	100
Noradrenaline	1000
<i>l</i> -Adrenaline	1077

The sympathomimetic action of natural and synthetic hydroxytyramine has been studied by Raymond-Hamet (129).

2. HALOSTACHINE

The pharmacological action of the natural alkaloid is similar to that of ephedrine (18). The racemic synthetic compound had already been examined by Barger and Dale. Hyde, Browning, and Adams prepared a series of homologues of *d,l*-ephedrine, in which the alkyl group on the β -carbon was replaced by H, ethyl, and *n*-propyl. The only homologue that gave a dependable increase in blood pressure was the α -phenyl- β -methylaminoethanol, i.e., racemic halostachine (20).

3. HORDENINE

The pharmacological action of anhaline (hordenine) was first described by Heffter (49). In frogs it causes paralysis of the central nervous system without previous excitation. Camus (130-133) reported that the compound is slightly antiseptic; it also has an inhibitory effect on some soluble ferments. In mammals it shows relatively low toxicity. Small doses have no effect on the circulation of the blood; larger ones raise the blood pressure and accelerate the pulse; in very large doses hordenine causes death by arrest of respiration.

Rietschel (134, 135) found that the pressor effect is not of central origin and that hordenine stimulates the heart muscle. Although much less active than adrenaline, it is analogous in its action, resembling ephedrine rather than adrenaline. According to Raymond-Hamet (136-138) and Ludueña (139), hordenine displays a nicotine-like action.

In large doses it decreases or reverses the hypertensive effect of adrenaline (Raymond-Hamet, 140).

4. CANDICINE

This alkaloid was first examined by Barger and Dale (2), and its pharmacological properties were thoroughly studied by Lewis and Ludueña (141, 142) as well as by Ludueña (139, 143-147).

Candicine displays a nicotine-like action on the visceral nervous system, first stimulating and then blocking the ganglionic synapse. It has no muscarine-like effect. In the dog, intravenous injection provokes hypertension owing to vasoconstriction due to stimulation of vasoconstrictor nerves and secretion of adrenaline from the adrenal gland. The adrenaline secretory effect is not modified significantly by yohimbine, cocaine, or atropine. Sparteine and tetrapropylammonium iodide completely counteract this effect. Large doses (6 mg./kg.) of candicine have a curare-like action in the dog; this effect has also been observed in the toad, *Bufo arenarum*. The LD₅₀ is 5 mg. per 100 g. for the rat, death occurring owing to respiratory paralysis.

5. CORYNEINE

Coryneine had already been examined by Barger and Dale (1); further data were given by Reti, Arnolt, and Ludueña (94). The action is very similar to, but more intense than that of candicine.

6. MESCALINE

The sliced and dried heads of the cactus, *Anhalonium lewinii* (*Lophophora williamsii*) have long been used as an intoxicant by the natives of Mexico and the southwestern part of the United States. Interest in the cactus alkaloids arose when the remarkable use by the Indian tribes and the strange pharmacological properties of this little plant became known.

The chroniclers of the Spanish conquest of Mexico are the first who mention this drug and describe its use and properties. Bernardino de Sahagun, a Franciscan monk and missionary, writes as follows in his "Historia General de las Cosas de Nueva Espana" (the manuscript, dated 1560, was only printed in 1829): "There is another plant like earth nopal, called peyote; it is white, grows in the Northern parts, and produces in those who eat or drink it terrible or ludicrous visions; the inebriation lasts for two or three days and then disappears. The Chichimecas eat it commonly, it gives them strength and incites them to battle, alleviates fear, and they feel neither hunger nor thirst, and they say it protects them from every kind of danger."

This first reference to peyote summarizes in a remarkable manner all our knowledge on the nature of this astonishing drug. Sahagun also points out accurately the botanical nature of the plant which is a "tuna de la tierra," i.e., a cactus. The word "tuna," of Mexican origin, is used in Spanish America to indicate cacti only. The use of the "satanic plant" called peyote is mentioned by Cárdenas, Francisco Hernández, and several other chroniclers of the Spanish conquest. The use and cult of the peyote remained alive among the Indian tribes of the area mentioned in spite of church and state prohibitions. Merchants in Indian territories call it mescal or mescal buttons, the Mexicans on the Río Grande, pellote, peyote or peyotl. Petrullo reported (148) that in 1918 a numerous sect, restricted to Indians, was founded in Oklahoma. It was called the "Peyote-Church" and joined in a strange synthesis of old Mexican, Christian, and local religious rites.

Further details and bibliography on the uses and religious cult of the peyote will be found in Lewin (149-152), Mooney (153), Diguët (154), Lumholtz (155), Newberne and Burke (156), and especially in the books by Rouhier (157) and Beringer (158).

Up to 1886 nothing was known of the nature and character of the "mescal buttons." At that time Louis Lewin, travelling in America, came to know the plant and obtained specimens that he examined. Hennings recognized it as a new species of *Anhalonium* and named the plant *Anhalonium lewinii*. Lewin's examination showed that the drug contained alkaloids, and a crystallized base, anhalonine, was isolated. However, anhalonine is not responsible for the sensory excitation caused by peyote. Lewin's discovery raised considerable interest in the pharmacological effect of the drug and in the chemical compounds that account for it. This interest was extended to the whole family of the Cactaceae, which, until then, had been considered as being free of alkaloids.

The most striking physiological effect of the pellote is the production of *visual color hallucination*. According to Heffter (105), among the pellote alkaloids only mescaline is responsible for these symptoms although Lewin (150) attributes a certain hallucinatory power to anhalonidine. Taking into account the high percentage of isoquinoline bases in pellote and their strong toxicity, the effects of intoxication by pellote are evidently not identical with those produced by the administration of pure mescaline. Nevertheless, in both cases, the visual hallucinations, described by different observers are of a similar nature.

Pellote inebriation has been described by numerous authors such as Prentiss and Morgan (159, 160), Heffter (105), Weir (161), Havelock (162), Rouhier (157), Hobschette (163), and others. The action of pure mescaline salts was reported by Dixon (164), Buchanan (165), Foerster

(166), Beringer (158), Marinesco (167), etc. In Beringer's book (158) numerous cases are reported and a full bibliography is given.

Marinesco (168) has also published an interesting study in which the impressions of two artists during mescaline intoxication are described, and six colored plates, painted during the effect of the drug, are reproduced.

Color visions were provoked by doses of 0.36–0.44 g. of mescaline sulfate distributed in several subcutaneous injections. The state of intoxication and the visions lasted for 5 to 10 hours. The effects varied widely in different individuals. The most characteristic symptom is that of wonderful visual color hallucinations. Clear consciousness is generally preserved and the subject is fully aware of his condition. Sensory illusions and transposition of sensorial excitation are the interesting factors in this inebriation. Ordinary objects appear to be marvelous. Sounds and music are "seen" in color. In comparison, the impressions of everyday life seem pale and inert. Color symphonies and new, unknown colors of unimaginable beauty and brilliancy are perceived. Euphoria is not always present. Hallucinations of hearing, taste, or other senses were reported more rarely. Bradycardia, nausea, a feeling of oppression in the chest, faintness, and headache may also occur.

The interest in these remarkable properties of mescaline has led to the synthesis of numerous similar compounds (p. 325). However, the slightest structural changes destroy the typical effects of mescaline. Until now no natural or synthetic compound with the pharmacological properties of mescaline has been found.

In the frog, mescaline causes narcotic effects (dose, 15 to 30 mg.). In rats the lethal dose is 20 mg./100 g. (Ludueña). Rabbits are extraordinarily resistant to mescaline (Slotta and Müller, 121); injection of even 0.1–0.25 g. of the hydrochloride per kilo body weight causes no visible symptoms. Dogs and particularly cats are more sensitive. A dog after having received a dose of 0.2 g. of mescaline hydrochloride showed the following strange behavior: the dog started to whine and bark, not at the observer but towards the opposite side of the cage; when called, it turned and wagged its tail.

Raymond-Hamet (169, 170) found that small doses of mescaline do not have any effect on the blood pressure of dogs while larger ones (20 mg./kg.) caused hypotension. Mescaline is antagonistic to the pressor action of adrenaline and the subsequent vagal effect. Slotta and Müller (121) observed that 40 to 50% of the mescaline fed to rabbits is excreted in form of trimethoxyphenylacetic acid; the latter is not found in human urine after the administration of mescaline. According to Richter (171) mescaline is excreted by humans unchanged, at least to a high extent (recovery, 58%). Bernheim and Bernheim (172) studied the mecha-

nism of mescaline oxidation in the rabbit. Grace (122) observed that intravenously injected mescaline produces respiratory depression and fall in blood pressure in anesthetized cats and dogs. It stimulates the contractions of the intestine and uterus *in situ* but not that of the isolated organs.

7. TRICHOCEREINE

Trichocereine was first examined by Ludueña (173). The lethal dose in the rat is approximately 22 mg. of hydrochloride per 100 g. weight. In this animal trichocereine causes excitation, tremor convulsions, paralysis of the extremities, and respiratory paralysis. In dogs large doses provoke a fall in blood pressure. Ingestion of 0.55 g. had no apparent effect in a self experiment of Ludueña, particularly no effect of a sensory nature.

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CHAPTER 23

Ephedra Bases

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	<i>Page</i>
I. Introduction	339
II. Occurrence.	340
III. Extraction and Separation	343
IV. Detection and Determination.	344
V. Physical and Chemical Properties	344
1. Ephedrine	344
2. ψ -Ephedrine	347
3. <i>l</i> -nor-Ephedrine.	348
4. <i>d</i> -nor- ψ -Ephedrine.	348
5. <i>N</i> -Methylephedrine.	348
6. <i>N</i> -Methyl- ψ -ephedrine.	349
7. Ephedine	349
8. Benzylmethylamine.	349
VI. Constitution and Spatial Configuration.	349
VII. Synthesis of the Ephedra Bases.	351
VIII. Pharmacology.	353
IX. References	355

I. Introduction

The herb called "Ma Huang" has been used in China for some five thousand years in the treatment of a variety of afflictions. A Chinese dispensatory, written in A.D. 1596, states that the plant is useful as a circulatory stimulant, diaphoretic, antipyretic, and sedative in cough, all of which has been confirmed by modern observations (1). Ephedras have been employed as remedies in many other parts of the world.

An active, impure principle was separated from "Ma Huang" in 1885 by G. Yamanashi, but a pure basic substance was isolated first by Nagai in 1887 (2) and called ephedrine. Takahashi and Miura (3) investigated ephedrine physiologically in 1888, and concluded that it dilated the pupil by stimulation of the sympathetic nerves. The substance was subsequently introduced into medicine as a new mydriatic, but its use soon disappeared and for many years its pharmacological study was practically abandoned.

However, investigations on ephedrine and related compounds were continued from a chemical point of view. Merck found ephedrine (4)

and ψ -ephedrine (5) in the European species, *Ephedra helvetica* C. A. Mey, as early as 1889. Ladenburg and Ölschlägel (6) working on ψ -ephedrine, proposed the presently accepted structure. Important studies on the constitution of ephedrine and ψ -ephedrine have been contributed by Nagai (7-17), Miller (18), Schmidt and coworkers (19-31), Emde and coworkers (32-46), Fourneau and coworkers (47-55), Rabe (56), Ogata (57), Freudenberg and coworkers (58-61), Leithe (62, 63, 64), and others.

The first attempts to synthesize ephedrine were by Schmidt in 1905 (20). Nagai, in 1911 (14) succeeded in a synthesis of racemic ephedrine. A similar result was achieved by Eberhard (65, 66, 67) and Fourneau (49). In 1920 Späth and Göhring (68, 69) described their success in the synthesis and separation of all six isomers. New syntheses of ephedrine have been described more recently by Späth and Koller (70), Fourneau and Torres (51), Kanao (71, 72, 73) (confirming the results of Späth and Göhring), Manske and Johnson (74, 75), Coles, Manske, and Johnson (76), Skita and Keil (77, 78, 79), Sah (80), and others.

The pharmacology of ephedrine was reinvestigated in Japan by Amatsu and Kubota (81), who demonstrated the adrenaline-like effects of the alkaloid, a conclusion also reached by other oriental workers. Since the results were published in Japanese, little attention was paid to them in the Western world.

A revolutionary renewal of the interest on ephedrine started in 1924 with the publication of the papers of Chen and Schmidt on Ma Huang (82-86). They worked on the drug without knowledge of previous work, and recorded the similarity of the physiological action of ephedrine and adrenaline. Since then an enormous volume of literature has accumulated on the chemistry and pharmacology of ephedrine and related natural alkaloids and synthetic compounds.

Monographs and summaries on ephedrine and related compounds have been published by E. Schmidt (87), Chen and Schmidt (86), Emde (44, 45, 46), Cheramy (88), Jackerott (89), Read (90), Gaddum (91), Hiner (92) and Henry (93).

II. Occurrence

Ephedra is the largest genus of the Family Gnetaceae (Order, Gnetales, Gymnosperms) with about 45 species, according to the Index Kewensis. However, Engler and Prantl (1926) admit only 35. *Ephedras* are found in the temperate and subtropical regions of Europe, Asia, and America.

Only a few of these species contain alkaloids. The best known source of ephedrine is the chinese drug "Ma Huang." It was formerly

classified as *E. vulgaris* var. *helvetica* Hooker and Thomson, but this name has been obsolete since 1927 (94, 95). Read and Liu (97) traced the botanical origin of Ma Huang to *E. equisetina* Bunge and *E. sinica* Stapf (*E. flava* F. Porter Smith, *E. Mahuang* Liu). The same authors later identified another species in Ma Huang, namely *E. distachya* L. (98, cf. also Gilg and Schürhoff, 99). More detailed information on Ma Huang can be found in the papers of Read and Feng (100–107), Chen (108), and others (109–112).

Read and Feng (113) examined three or four species of *Ephedra* growing in northern India: *Ephedra intermedia* Schrenk and C. A. Mey, *E. distachya* (*E. gerardiana* Wall.), *E. sinica*, and *E. equisetina*, all with high content of alkaloids. Krishna and Ghose (114) investigated the alkaloidal content of five Indian species: *E. distachya*, *E. nebrodensis* Tineo, *E. intermedia*, *E. pachyclada* Boiss., and *E. foliata* Boiss. and Kotschy; —the last contains no ephedrine. Indian ephedras and their seasonal variations in the alkaloidal content was studied by Chopra, Ghosh and Dutt (115), Chopra and Dutt (116), Ghose and Krishna (117, 118), Chopra, Krishna and Ghose (119) and Quazilbash (120).

American ephedras are devoid of alkaloids (121–127), with the exception of *E. americana* Humb. & Bonpl. (*E. andina* Poepp. & Endl.) in which Chavez (128) found 0.38% of ephedrine. In the Southwestern states of the United States experiments have been carried out to acclimatize imported species (129–133).

In Australia, the cultivation of the Indian species *E. gerardiana*, *E. intermedia*, and *E. nebrodensis* has been tried with satisfactory results (145).

Black and Kelley (134) and Peronnet and Chatin (135) reported on the occurrence of ephedrine and ψ -ephedrine in the North-African *Ephedra alata* Decne. Massagetov (136) reported on two Russian species, *E. equisetina* and *E. intermedia*, as practical sources of ephedrine.

In Italy several investigations have been carried out by La Floresta (137, 138), Carboni (139, 140, 141) Mulas and Salis (142), Alberti (143) and Simon (144), on local species of Sardinia and Sicily, to find suitable sources of ephedra alkaloids. It was found that *E. nebrodensis* contained high amounts of ephedrine and ψ -ephedrine; *E. distachya* (*E. vulgaris* Rich.) contained only ψ -ephedrine, while *E. fragilis* Desf., *E. altissima* Desf., and *E. procera* C. A. Mey (*E. nebrodensis* Tineo?) were of low alkaloidal content.

There are wide variations between different species in total alkaloidal content and in the ratio of ephedrine to ψ -ephedrine. There are also great seasonal and environmental variations. A distinct increase in content of alkaloids is observed as the plant matures, attaining a maxi-

mum in fall. Older plants contain more alkaloids than young ones (97, 116, 132).

During the flowering season there is a greater amount of alkaloids in the male than in the female plant (105, 140, 144). Ephedras growing in moist places have a low content of alkaloids (117). The nodes contain only a third of the alkaloidal content of the internodes, but they contain a greater proportion of ψ -ephedrine than do the internodes. This is in accordance with the preference of the Chinese physicians for the internodes, for fear of the diaphoretic effect of ψ -ephedrine (101, 105). In the young herb the alkaloids are distributed evenly between pith and outer stem wall; in the mature plants the pith has a considerably higher alkaloidal content (112). There are no alkaloids in the roots, berries, or seeds of these plants (101, 105).

In specially collected ephedra plants total alkaloid yields as high as 3.4% have been observed (142). A good grade of Ma Huang should yield 2% of total alkaloids (111) but the commercial product usually contains about 1%.

The British Pharmaceutical Codex, 1934, specifies a total alkaloidal content of not less than 1.25%.

Several bases, other than ephedrine and ψ -ephedrine, have been identified in Ma Huang. Smith found *l*-*N*-methylephedrine (146) and nor-*d*- ψ -ephedrine (147) in the sirupy alkaloidal residue obtained in the manufacture of ephedrine. Nagai and Kanao (149), working up thoroughly a Ma Huang extract, confirmed Smith's observations and separated another new alkaloid, *d*-*N*-methyl- ψ -ephedrine. Kanao (150) succeeded in isolating a sixth ephedra base, *l*-norephedrine.

From Ma Huang there have also been isolated a volatile basic compound, benzylmethylamine, by Chen, Stuart and Chen (151) and ephedine, and an alkaloid of undetermined structure, by Chou and Chu (152). Wolfes (153) showed that the European ephedras contain the same alkaloids as the Chinese species.

Spehr (154) gave the name "ephedrine" to a base isolated from *E. monostachia* of unknown botanical authority, but the compound is chemically and physiologically different from *l*-ephedrine. The base, $C_{13}H_{19}ON$, melted at 112°, was freely soluble in water and yielded a hydrochloride melting at 207°.

Alkaloids of ephedrine-type have been found in plants botanically widely separated from the ephedras. Ephedrine has been isolated in very small quantities from the leaves of the yew, *Taxus baccata*, L., by Gulland and Virden (155). Ghosh and Dutt (156) identified ephedrine as a constituent of the alkaloid mixture extracted from the Malvaceae, *Sida cordifolia* L. Other alkaloids, related to ephedrine, are likely to be found in the same plant. Cathine, a base described by Bitter (157) and

Stockmann (158, 159), isolated from the Celastraceae, *Catha edulis* Forsk. has been shown by Wolfes to be *d*-nor- ψ -ephedrine (160).

Ephedrine occurs also in the Papaveraceae, *Roemeria refracta* D.C., as shown by Knovalova, Yunusov and Orekhov (161) and has been recognized in the so called "amorphous aconitine," which is a mixture of residual bases obtained in the commercial preparation of crystalline aconitine from *Aconitum napellus* L. (162). Freudenberg and Roger's previous statement (163), that *l*-ephedrine is a degradation product of the napellus alkaloids, has therefore to be revised.

According to Ghosh, Chopra, and Dutt (164) the bark of *Moringa pterygosperma* Gaertn. (Moringaceae) contains two alkaloids whose pharmacological action is similar to that of ephedrine.

III. Extraction and Separation

The ephedrine bases may be extracted from the plant material, following general procedures.

A method of extraction has been described by Chou (165): Powdered Ma Huang was extracted with cold benzene in the presence of diluted sodium carbonate. The benzene extract was extracted with dilute hydrochloric acid and the acid solution of the alkaloids clarified. After adding enough solid potassium carbonate to the acid solution, the alkaloids were extracted with chloroform. This solution was concentrated, dried over sodium sulfate, and evaporated to dryness. Ephedrine has been separated from ψ -ephedrine by means of the oxalate, the ephedrine salt being much less soluble in cold water.

Feng and Read (104) found that the low yield of alkaloids obtained by previous workers was due to incomplete alkalization of the herb before extraction with chloroform or ether. Hot extraction and the use of sodium hydrate to liberate the alkaloids has been found satisfactory. The ammonia-chloroform process has been critically studied and it was found that a large excess of ammonia was necessary to liberate the alkaloids. Feng (103) extracted *Ephedra equisetina*, first with 80% alcohol and finally with 0.2% acetic acid. After working up the extracts, ephedrine was separated from ψ -ephedrine by crystallization of the hydrochlorides from 95% alcohol. ψ -Ephedrine may be recovered from the mother liquors. Ghose and Krishna (114, 117, 118) described other methods of extraction and the preparation of alkaloid concentrates. They separated ephedrine from ψ -ephedrine by extracting the dry hydrochlorides with chloroform, in which only the ψ -ephedrine salt is soluble.

The separation of the six natural ephedra bases has been described by Kanao (150). *l*-Ephedrine was first separated as hydrochloride, then ψ -ephedrine as the free base, *l*-methylephedrine as the oxalate, *d*-methyl- ψ -ephedrine as the *d*-bitartrate and finally nor-*d*- ψ -ephedrine, from

alcohol, as the sulfate. Norephedrine, which crystallizes together with nor-*d*- ψ -ephedrine was separated in the form of its *l*-bitartrate.

IV. Detection and Determination

Numerous methods have been devised for the identification and determination of ephedrine and related alkaloids. Ephedrine and ψ -ephedrine give precipitates with some alkaloidal reagents (166, 167). Several color reactions of the ephedra-bases have been described (168–176). The most serviceable is that with copper sulfate-sodium hydroxide (biuret reaction) (104, 177–179), which has been elaborated by Feng to a quantitative colorimetric test (178). Sivadijan's test (180, 181, 182) is based on a red-violet color produced by heating a solution of ephedrine salts, with hydrogen peroxide, sodium chloride, and sodium hydroxide. The reactions, as well as that of Fourment and Roques (183), who use an alkaline 1% solution of osmium tetroxide, giving orange and yellow precipitates, have been proposed to differentiate ephedrine from ψ -ephedrine.

There are several papers dealing with the microchemical identification of the ephedrine bases (99, 184–196).

The quantitative estimation of ephedrine and ψ -ephedrine can be performed in several ways. The extracted or steam distilled alkaloids may be estimated gravimetrically by weighing the free bases (197, 198) or by Jackerott's method, weighing the hydrochloride (199, 200, 201). However, the estimation is performed generally by alkalimetric methods (111, 130, 202–213) using methyl-red or bromothymol-blue as indicator. Sanchez (214, 215) proposed a quantitative test, based on the formation of iodoform when ephedrine is heated with potassium hydroxide, iodine, and potassium iodide. Wickström (216) elaborated a similar method, based on the formation of acetaldehyde by the oxidation of ephedrine with periodic acid. Various other chemical methods as well as comparative studies on the estimation of ephedrine have been published (92, 217–223). Biological assays are also possible but with less satisfactory results (224, 225). More recently, chromatographic methods have been proposed for the resolution, analysis and separation of the ephedrine bases (226–230). Also ion-exchange resins (231, 232, 233) and electro-dialysis (234) have been employed for the same purpose. Ephedrine is polarographically inactive (235).

V. Physical and Chemical Properties

1. EPHEDRINE (*l*-EPHEDRINE), $C_{10}H_{15}ON$

The free base (anhydrous) has m.p. 38.1°; the hemihydrate, m.p. 40°. With 1.5% water, a eutectic mixture, ephedrine-ephedrine hydrate, with m.p. 32.1°, is obtained. The b.p. of anhydrous ephedrine is 225°

(760 mm.) and 152–153° (25 mm.) (236–237). However, ephedrine is volatile even at room temperature; a sample exposed by Read to the air showed a loss of 33% after 4½ months (107). It is rapidly volatile at 100° and therefore is volatile with steam (238).

Ephedrine shows $[\alpha]_D^{20} - 6.3^\circ$ (hemihydrate in alcohol) or $[M]_D^{20} + 18.5^\circ$ (water). It is soluble in water, alcohol, ether, chloroform, and oils (239). The solution in water is strongly alkaline to litmus paper. The hydrochloride, $C_{10}H_{15}ON \cdot HCl$, is in the form of white, prismatic needles of bitter taste, m.p. 220–221°; $[\alpha]_D^{20} - 34^\circ$ (H_2O); soluble in 2 parts of water and in 15 parts of alcohol (95°). The hydrobromide has m.p. 205°. The hydrobromide and the hydrochloride, unlike the corresponding ψ -ephedrine salts, are very sparingly soluble in chloroform (30). The hydriodide, from acetone, has m.p. 165° (43). The sulfate is in the form of hexagonal plates, m.p. 247°; $[\alpha]_D^{25} - 32^\circ$, soluble in four parts of water, sparingly soluble in alcohol. The phosphate is in the form of long silky needles, m.p. 178° (165); the aurichloride, yellow crystals, m.p. 130–131°; the platinichloride, m.p. 186° (240); *l*-ephedrine-*d*-bitartrate, m.p. 69° (71); the oxalate, prismatic needles, m.p. 249°, sparingly soluble in cold water. The *N*-*p*-nitrobenzoyl derivative has m.p. 187–188; nitrosamine, m.p. 92°. *N*-Carbethoxy derivative has b.p. 169–171° (1–2 mm.); 3,4-dimethyl-5-phenyl-2-oxazolidone from ephedrine, m.p. 57–58° (249). Methylephedrine methiodide has m.p. 212–213° (244).

Ephedrine and ψ -ephedrine are quite stable compounds. Heating at 100° for 24 hours causes no decomposition (42, 28). No alteration is observed by heating the bases with 5% sodium hydroxide on the water bath (21). Unsuccessful attempts were made to racemize ephedrine and ψ -ephedrine with barium hydroxide or alcoholic potassium hydroxide (25). However, in the patent literature statements have been made that the optically active forms of the bases can be racemized by heating them with alkali alcoholates, at temperatures ranging from 168 to 195°, in the molten state, or in a solvent (274, 275). Ephedrine solutions are unstable in sunlight in the presence of oxygen (276).

On heating ephedrine hydrochloride with 5% hydrochloric acid, under pressure, at 170–180° (248) or with 25% acid, at 100°, the compound is partially converted to ψ -ephedrine (20, 32, 40). The conversion is reversible and an equilibrium is established. According to Emde (39), the rearrangement takes place by replacement of the hydroxyl group by chlorine, followed by hydrolysis. Oxidation of ephedrine or ψ -ephedrine, gives benzaldehyde or benzoic acid.

By the reduction of ephedrine or ψ -ephedrine, the same deoxyephedrine, $C_{10}H_{15}N$ is obtained (29, 39). Hydrochloride has m.p. 172°, $[\alpha]_D^{7.5} + 17.8^\circ$; platinichloride, m.p. 208–209°; aurichloride, m.p. 126°.

The action of acetic anhydride on ephedrine and ψ -ephedrine was studied by Miller (18) and later by Mitchell (241) and by Welsh (242). The reaction leads, depending on the experimental conditions, to mixtures of *N*-acetyl and *O*-acetyl compounds. According to Welsh, ephedrine heated at 70° with acetic anhydride, gives 93% of *N*-acetylephedrine, m.p. 85.5–86.5°. *d,l*-Ephedrine, under similar conditions, gives an *N*-acetyl derivative, m.p. 77–78.5°. This acetyl ephedrine combines with hydrochloric acid to form an addition compound having a strongly acid reaction: the combined hydrogen chloride can be directly and quantitatively titrated with alkali using methyl red or phenolphthalein as indicator. The unaltered acetyl derivatives can be recovered from these hydrogen chloride-adducts by solvent extraction after adding excess alkali to the aqueous solutions. *N*-Acetyl-*d,l*-ephedrine, on standing in acetone solution containing hydrochloric acid for 6 days at room temperature, gives 74.8% *O*-acetyl-*d,l*-ephedrine hydrochloride, m.p. 201–201.5°. In the presence of alkali, this salt rearranges quantitatively to the *N*-acetyl compound, without change in configuration. It has not been possible to prepare analogously the *O*-acetyl-*l*-ephedrine hydrochloride, owing apparently to the difficulty of inducing it to crystallize (Phillips and Baltzly (277), Kanao (71, 73), and Fodor and coworkers (252)). *N*-Acetyl-*l*-ephedrine hydrochloride, when heated at 110°, gives 51.6% of *O*-acetyl-*d-ψ*-ephedrine, while *l*-ephedrine hydrochloride, heated with acetic anhydride, yields 52.5% of *O*-acetyl-*d-ψ*-ephedrine. Hydrolysis of *N*-acetyl-*l*-ephedrine, by refluxing with 5% hydrochloric acid, leads to a mixture of the hydrochlorides of *l*-ephedrine and *d-ψ*-ephedrine; this inversion accompanies the *N* → *O* shift of the acetyl group prior to hydrolysis, and is not due to the action of the acid on ephedrine.

Feng and Wilson (243) prepared some tertiary amines derived from ephedrine; the quaternary ammonium halides of ephedrine have been described by Feng (244).

A peculiar property of ephedrine is its rather violent reaction with chloroform; by evaporation of a solution of ephedrine in this solvent, ephedrine hydrochloride and aldehydes are formed. Chloroform thus can not be considered a suitable medium for the extraction and the estimation of ephedrine (245, 246).

According to Davies (247) ephedrine reacts with benzaldehyde, giving 2,5-diphenyl-3,4-dimethyltetrahydroöxazole, m.p. 73.5°. The "benzalephedrine" of Schmidt (30) should be identified with this compound.

d-Ephedrine has not been found naturally. The synthetic base has m.p. 40–40.5°; the hydrochloride is in the form of white leaflets, m.p. 216–217°, $[\alpha]_D^{20} + 34.42^\circ$; *N-p*-nitrobenzoyl derivative is in the form of

prisms, m.p. 187–188°; *d*-ephedrine-*d*-bitartrate has m.p. 145–146° (68, 71).

dl-Ephedrine (racemic ephedrine), is the synthetic, inactive ephedrine of commerce. The free base has m.p. 76–78°; hydrochloride, m.p. 187–188°; platinichloride, m.p. 186°; aurichloride, m.p. 112–113°; dimethylammonium iodide, m.p. 228–229°; *N*-*p*-nitrobenzoyl derivative, m.p. 162° (71).

2. ψ -EPHEDRINE (*d*- ψ -EPHEDRINE), $C_{10}H_{15}ON$

The base forms white rhombic crystals, m.p. 118° (from water); $[\alpha]_D^{20} + 51.2^\circ$ (alcohol) and is much less soluble in water than ephedrine. Hydrochloride, colorless needles, m.p. 181–182°; $[\alpha]_D^{20} + 62.5$ (water); the salt is soluble in chloroform. Hydriodide, rhombic crystals, m.p. 172°; $[\alpha]_D^{20} + 43.0^\circ$ (43). Oxalate, needles, m.p. 219° (165), readily soluble in water. Nitroso- ψ -ephedrine, m.p. 86°.

With acetic anhydride, ψ -ephedrine reacts much like ephedrine (241, 242). According to Welsh, the product of the reaction, at 70° is *N*-acetyl-*d*- ψ -ephedrine, m.p. 103.5–104°; $[\alpha]_D^{20} + 110.4^\circ$ (50% alcohol). The hydrochloric acid adduct (hydrochloride), has m.p. 180°; $[\alpha]_D^{20} + 93.3^\circ$ (50% alcohol). On heating at 110°, this hydrochloride yields 88.4% of *O*-acetyl-*d*- ψ -ephedrine hydrochloride, m.p. 179.5–181; $[\alpha]_D^{20} + 98.6^\circ$ (water). The same compound is obtained by adding concentrated hydrochloric acid to *N*-acetyl-*d*- ψ -ephedrine dissolved in acetone. On boiling *N*-acetyl-*d*- ψ -ephedrine or *O*-acetyl-*d*- ψ -ephedrine hydrochloride with 5% hydrochloric acid, ψ -ephedrine is quantitatively regenerated (unlike the ephedrine compound). The *O*-acetyl compound of ψ -ephedrine, like that of ephedrine, in the presence of alkali rearranges to the *N*-acetyl compound, without change in configuration. This rearrangement is much more rapid in the ψ -ephedrine derivatives than in those of ephedrine. The speed of the rearrangement depends on the H-ion concentration and is instantaneous at high pH.

l- ψ -Ephedrine has not been found in nature. The base has m.p. 118–118.7°; $[\alpha]_D^{22.5} - 52.50^\circ$ (alcohol). The hydrochloride has m.p. 182–182.5°; $[\alpha]_D^{20} - 62.1^\circ$. The *l*- ψ -ephedrine-*d*-tartrate has m.p. 178°; *l*- ψ -ephedrine-*l*-tartrate, m.p. 178.5°; phenylthiourea, m.p. 120–121°; *N*-*p*-nitrobenzoyl derivative, m.p. 177° (17, 68, 69, 70).

dl- ψ -Ephedrine (racemic ψ -ephedrine) melts at 118°. The hydrochloride has m.p. 164°; aurichloride (abnormal), $(C_{10}H_{15}ON)_2HCl \cdot HAuCl_4$, m.p. 186–187° (68, 69, 70). The oxalate has m.p. 218°; *N*-*p*-nitrobenzoyl derivative, m.p. 165–166°; dimethylammonium iodide, m.p. 183° (17).

3. *l*-NOR-EPHEDRINE, $C_9H_{13}ON$

This was isolated by Kanao (150) from a Ma Huang grown at Pechili and found by Wolfes (153) in the European *Ephedra*. It was synthesized previously by Kanao (72, 73) and by Nagai and Kanao (17). The free base has m.p. 50–52°; $[\alpha]_D^{17} - 14.8^\circ$ (alcohol absol.). The hydrochloride has m.p. 172°; $[\alpha]_D^{20} - 33.14^\circ$; sulfate, m.p. 285–286°; $[\alpha]_D^{28} - 31.39^\circ$ (water); platinichloride, m.p. 221.5°; aurichloride, m.p. 188°; *N*-*p*-nitrobenzoyl derivative, m.p. 175–176°. The *l*-bitartrate, m.p. 160°; $[\alpha]_D^{33} - 34.64$ (water) is well adapted for the separation of the base. In the cited papers of Kanao and Nagai, the characteristics and constants of synthetic *dl*- and *d*-norephedrine, as well as those of *dl*- and *l*-nor- ψ -ephedrine are given.

4. *d*-NOR- ψ -EPHEDRINE, $C_9H_{13}ON$

By working up the sirupy residue obtained in the manufacture of ephedrine from Ma Huang, Smith (147) first isolated the base as sulfate. The synthesis was achieved by Kanao (72, 73) and by Nagai and Kanao (17).

The free base crystallizes in plates, m.p. 77.5–78°; $[\alpha]_D^{20} + 37.9$ (methanol); the hydrochloride, prisms, m.p. 180–181°; $[\alpha]_D^{20} + 43.2^\circ$ (water); sulfate, hexagonal plates, m.p. 295; $[\alpha]_D^{20} 48.7^\circ$ (water); aurichloride, m.p. 137–138°; platinichloride, m.p. 198°; oxalate, m.p. 235°; *l*-bitartrate, m.p. 202°; $[\alpha]_D^{20} + 13.36$ (water). The dibenzoyl derivative, m.p. 156–157°, on partial hydrolysis with potassium hydroxide in methanol, gives *N*-benzoyl-*d*-nor- ψ -ephedrine, m.p. 132°. This compound reacts with hydrochloric acid in acetone solution, giving *O*-benzoyl-*d*-nor- ψ -ephedrine hydrochloride, m.p. 244–245°, which, treated with sodium hydroxide, regenerates the *N*-benzoyl derivative. This behavior is similar to that of the acetyl derivatives of ephedrine and ψ -ephedrine, described by Welsh (242), Nagai and Kanao (17), and Kanao (72, 73). McKenzie, Luis, and Mitchell (148) studied the action of nitrous acid on salts of *d*-nor- ψ -ephedrine. Gibson and Levin (250) considered *d*-nor- ψ -ephedrine as a convenient base for the resolution of externally compensated acids, such as *dl*-benzenesulfonylalanine and *dl*-*N*-phenylalanineamido-4-arsonic acid.

5. *N*-METHYLEPHEDRINE (*l*-*N*-METHYLEPHEDRINE), $C_{11}H_{17}ON$

This alkaloid was found by Smith (146) in Ma Huang and by Wolfes in European *Ephedra* and isolated from the residue of the ephedrine manufacture with aid of the picrate, m.p. 144°. It was synthesized and

described by Nagai and Kanao (17) and by Feng and Wilson (243). The base forms sturdy needles, m.p. 87–88°, b.p. 137–139° (14 mm.) The hydrochloride has m.p. 192°; $[\alpha]_D^{20} - 29.8^\circ$ (water); methiodide, m.p. 212–213° (244); aurichloride, m.p. 128–129°; oxalate, m.p. 187°.

6. *N*-METHYL- ψ -EPHEDRINE (*d-N*-METHYL- ψ -EPHEDRINE), $C_{11}H_{17}ON$

N-Methyl- ψ -ephedrine was isolated by Nagai and Kanao (149) from Ma Huang grown in the Pechili district. It was first synthesized by Emde (32) and later by Smith (147) and by Nagai and Kanao (17). The base crystallizes in needles with a flowery odor, m.p. 30°, b.p. 145° (24 mm.), $[\alpha]_D^{21} 48.1^\circ$ (methanol). The aurichloride has m.p. 126–127°; methiodide, m.p. 216–217°; bitartrate, $2H_2O$, m.p. 84°; bitartrate (anhydrous), m.p. 152°; picrate, m.p. 152–153°.

7. EPHEDINE, $C_8H_{18}N_2O_3$

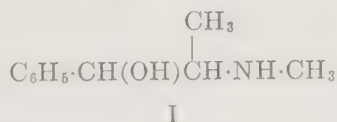
Ephedine was discovered in Ma Huang, by Chou and Chu (152) and is an alkaloid of undetermined structure. The base, m.p. 76°, is optically inactive. It forms a hydrochloride, m.p. 90°; picrate, m.p. 190°; and platinichloride, m.p. 280°.

8. BENZYL METHYLAMINE, $C_8H_{11}N$

Benzylmethylamine was identified in Ma Huang by Chen, Stuart and Chen (151). Oily base, $D_{15}^{18.5}:0.9450$; b.p. 180–181° (765 mm.). The hydrochloride forms fine plates, m.p. 180.5°; soluble in water, alcohol, chloroform; only slightly soluble in ether, acetone, and petrolether. The aurichloride has m.p. 139–140°; platinichloride, m.p. 194–195°; sulfate, m.p. 144.2°; oxalate, m.p. 201°.

VI. Constitution and Spatial Configuration

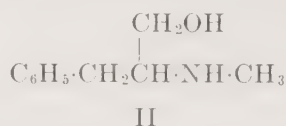
Ladenburg and Ölschlägel (6), working on ψ -ephedrine in 1889 demonstrated the presently accepted structure:



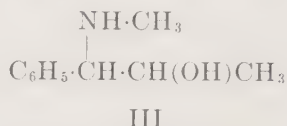
It was shown that ψ -ephedrine is a secondary amine, containing an alcoholic hydroxyl group, as indicated by the formation of a nitrosamine and a dibenzoyl derivative. The presence of a methyl group is evident from the appearance of methylamine by oxidative or degradative reac-

tions. The ease with which ephedrine and ψ -ephedrine are oxidized to benzaldehyde or benzoic acid points to a hydroxyl attached to the carbon adjacent to the benzene ring.

However, misled by the abnormality of some chemical reactions, Miller (18) in 1902, suggested a different structure,



and a third one was preferred by Emde in 1907 (34):



Emde suggested that ephedrine and ψ -ephedrine are stereoisomerides, a fact supported by the ease with which ephedrine is converted to ψ -ephedrine and particularly by the reversibility of this reaction, which was confirmed by Gadamer (251).

To clarify the situation Schmidt (22) in 1909 reported a decisive experiment on distillation of ephedrine hydrochloride in an atmosphere of carbon dioxide. Methylchloride and propiophenone are formed, a reaction compatible only with structure I.

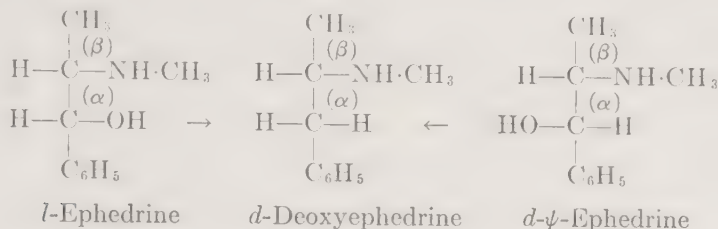
Rabe's (56) and Schmidt's (24) experiments, that is, decomposition of the trimethylammonium hydroxides of ephedrine and ψ -ephedrine, to stereoisomeric 1-methyl-2-phenylethylene oxides, lead to the same inference. This hydramine degradation occurs in compounds with vicinal hydroxyl and amino groups, and is indicated by the reaction scheme on p. 362.

Further contributions supporting structure I for ephedrine and ψ -ephedrine have been made by Schmidt (30, 31), Eberhard (65-67), Ogata (57) and others. Ogata arrived at the correct structure by the study of deoxyephedrine. Numerous syntheses finally proved the correctness of Ladenburg and Ölschlägels first formula.

Structure I contains two dissimilar asymmetric centers so that four optically active isomers and two racemic forms are possible. The naturally occurring *l*-ephedrine and *d*- ψ -ephedrine are not optical antipodes, but mutually interconvertible diastereoisomers. The other possible forms are known only as synthetic compounds.

The stereoisomerism between ephedrine and ψ -ephedrine is due to the difference in configuration about the α C'-atom, while the asymmetry about the β C'-atom is identical in both compounds since the reduction of

both leads to the same *d*-deoxyephedrine, as shown by Schmidt (29, 31) and by Emde (39).

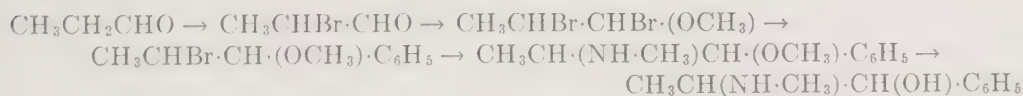


The problem of the configuration of the ephedrine molecule is not yet settled and has been studied particularly by Emde (34, 35, 36, 39-43, 46), Gadamer (251), Schmidt (30, 31), Leithe (62, 63, 64), Skita and coworker (79), Freudenberg and coworker (58, 59, 61), and recently, by Fodor and coworker (252), and by Close (254).

Crystallographic studies on the optically active forms of ephedrine and ψ -ephedrine derivatives have been carried out by Emde and Spaenhauer (43), Brückl (255) and by Gossner and Neff (256-260).

VII. Synthesis of the Ephedra Bases

The first attempts to synthesize ephedrine were by Fourneau (47, 48) in 1904, followed by Schmidt (19, 22, 24, 25) in 1905. Nagai (14) in 1911 achieved a synthesis of racemic ephedrine, but the fact has not been duly credited in the literature. Eberhard (65, 66, 67) obtained racemic ephedrine and ψ -ephedrine in 1917 by hydrogenation of α -methyl-amino-propiophenone. In 1920, Späth and Göhring (68, 69) synthesized ephedrine, ψ -ephedrine, their optical antipodes, and racemic compounds. Propionaldehyde was first brominated and the monobromo-derivative reacted with methanol and hydrobromic acid yielding 1,2-dibromo-1-methoxypropane, which in turn with phenylmagnesiumbromide gave an addition product which after hydrolysis yielded 1-phenyl-1-methoxy-2-bromopropane. This was converted by methylamine into 1-phenyl-1-methoxy-2-methylaminopropane, which on hydrolysis with hydrobromic acid, yielded 1-phenyl-1-hydroxy-2-methylaminopropane, i.e., racemic ψ -ephedrine.



The racemic base was resolved, by crystallization of the tartrates, into *l*- and *d*- ψ -ephedrine. By isomerization of both forms, with hydrochloric acid, *l*- and *d*-ephedrine were obtained.

Fourneau and Puyal (49) prepared methylstyrene by dehydration of

phenylethylcarbinol. The corresponding bromohydrin was reacted with methylamine; several isomeric ephedrine were obtained. The compound of m.p. 60° was shown later by Fourneau and Kanao (50) to be isoeephedrine, corresponding to structure III of Emde (51).

In 1925 Späth and Koller described a new ephedrine synthesis. α -Phenylpropylene was reacted with bromine to 1-phenyl-1,2-dibromopropane. One bromine was then substituted by methoxyl, the other by $\text{NH}\cdot\text{CH}_3$. On hydrolysis with fuming hydrobromic acid, racemic ψ -ephedrine was formed. (Compare also Späth and Bretschneider, 261.)

Kanao (71), in 1927, synthesized racemic ephedrine in excellent yields by methylating phenylpropanolamine or by reducing α -methylaminopropiophenone. The first compound had been prepared by condensation of benzaldehyde with nitroethane followed by reduction. Two amines were obtained, which by methylation gave racemic ephedrine and racemic ψ -ephedrine respectively. Nagai and Kanao (17) described the syntheses of the optically active ephedrines and those of the nor- and *N*-methylephedrines and ψ -ephedrines, following this method of preparation. Later, in 1947, Hoover and Hass (270) utilized the same reaction sequence to obtain the ephedrine bases.

The ephedrine synthesis described by Manske and Johnson (74) and by Skita and Keil (77) in 1929 is founded on a different reaction. If a mixture of α -phenylpropane- α,β -dione and methylamine, in absolute alcohol is hydrogenated catalytically in the presence of platinum oxide (Manske) or colloidal platinum (Skita), *dl*-ephedrine, with a little *dl*- ψ -ephedrine is obtained. The reaction has been further elaborated by Coles, Manske, and Johnson (76), by Skita, Keil and coworkers (78, 79, 262, 263) and by Couturier (265). Manske and Johnson (75) synthesized some ephedrine homologs and resolved racemic ephedrine by means of *d*- and *l*-mandelic acid. The pure *l* form of this acid is prepared easily with the aid of natural ephedrine, as confirmed by Jarowski and Hartung (268).

Freudenberg, Shoeffel, and Braun (59, 60), started from *d*(-) mandelic acid. The amide, with methylmagnesium iodide, gives *l*-phenylacetylcarbinol, which, by catalytic hydrogenation, in the presence of methylamine, yields *l*-ephedrine. Bossert and Brode (264) synthesized ψ -ephedrine by reacting 1-phenyl-1-ethoxy-2-bromopropane with methylamine, followed by hydrolysis. Sah (80) in 1938 reported a general method for the conversion of aminoacids into alkaloids of the ephedrine type. Benzylchlorocarbonate was condensed with alanine and the product transformed into the acid chloride. This substance, with phenylmagnesiumbromide, yielded a compound, which on catalytic hydrogenation with palladium and decomposition in toluene generated carbon dioxide and a mixture of racemic norephedrine and nor- ψ -ephedrine. Stevens and coworker (266, 267) studied the reduction of α -bromopropio-

phenone with aluminum isopropylate. A bromohydrin was obtained, which with methylamine gave a small yield of *dl*- ψ -ephedrine.

Fourneau and Benoit (55) investigated the action of methylamine on several forms of phenylpropylene oxide. A complicated mixture of ephedrines and isoephedrines was obtained.

According to Akabori and Momotani (269), a mixture of an aromatic aldehyde and an amino acid on heating yield alkamines. By means of this reaction, ephedrine and norephedrine were synthesized.

A very ingenious direct synthesis of *l*-ephedrine, avoiding the laborious resolution of the racemic mixture, has been devised by Hildebrandt and Klavehn (271) and described by Kamlet (272). Neuberg and Hirsch (273) in 1921 demonstrated that when equal mols of acetaldehyde and benzaldehyde are added to a carbohydrate solution actively fermenting by yeast, levorotatory 1-phenyl-2-ketopropanol-1, $C_6H_5 \cdot CH(OH)CO \cdot CH_3$, is formed. This compound on reaction with methylamine and catalytic reduction yields *l*-ephedrine directly.

Racemic ephedrine can be separated by chromatography into the optically active forms, according to Lecoq (226). Syntheses of homologs and isomers of ephedrine have been described by Schmidt and Calliess (25), Hyde, Browning, and Adams (281), Sánchez (282), Manske and Johnson (75), Fourneau and Barrelet (53), Fourneau, Benoit and Firmenich (54), Fréon and Ser (283), Kanao (278), Beals and Gilfillan (279), Wilson and Chang (280), Lozeron (284), Mannich and Budde (285), and Lambillon (286). Skita, Keil, and Meiner (79), prepared the nucleus-hydrogenated optically active hexahydroephedrines, by resolution of the racemic compounds with optically active mandelic acids.

VIII. Pharmacology

It is not within the scope of this study to offer exhaustive references on the enormous literature accumulated on the pharmacological action and clinical use of ephedrine and ephedrine-like compounds. Additional information may be found in the already cited surveys (p. 340). A symposium on sympathomimetic agents, with contributions by Gold, Hartung, Scholz, Tainter, Beyer and Morrison, Graham, Cartland and Woodruff, has been published in 1945 (287). Bayer's (288) and Mascherpa's (289) papers, Guggenheim's (290) book and the chapter on β -phenethylamines (pharmacology) of this book may be consulted for more information on sympathomimetic amines.

Ephedrine is essentially a sympathomimetic drug. The pharmacological effects of ephedrine resemble those of adrenaline, but various differences have been observed:

(a) Ephedrine is more stable and has a more prolonged action than adrenaline. Unlike adrenaline it is effective when given by mouth. The

rise in pressure produced by intravenous injections of adrenaline in cats is 100 to 142 times as intense as that of the same dose of ephedrine, but the effect of ephedrine persists 7 to 10 times as long as that of adrenaline, as shown by Chen and Kao (240) and by Nagel (291).

(b) The intensity of effect of adrenaline is so closely proportional to the injected quantity that the pressure response can be employed as quantitative analytical test. In the case of ephedrine there is no proportionality between circulatory effect and injected quantity (Chen and Schmidt, 82, 83).

(c) If the same dose of adrenaline is repeatedly injected, the same degree of effect will be obtained from each. With ephedrine the effect diminishes with each successive dose. This depression of the response lasts for only a few hours (82, 83).

(d) The action of ephedrine, unlike that of adrenaline, is not reversed by ergotoxine and other sympatholytic substances (Nagel, 291; Kreitmair, 292; De Eds and Butt, 293). Raymond Hamet (294) found that yohimbine exerts an action similar to that of ergotoxine.

(e) Cocaine potentiates the action of adrenaline, but reduces or abolishes that of ephedrine (De Eds, 293; Pak and Read, 295; Tainter, 296).

Ephedrine, in large doses antagonizes adrenaline (Schaumann, 297; Curtis, 298).

Gaddum (91), commenting on the investigations of Blaschko, Richter, and Schlossmann (299), discussed the theory that the action of ephedrine is based on the inhibition of an enzyme system, which normally destroys adrenaline. Ephedrine is not destroyed by amine oxidase, but in the presence of ephedrine the enzyme is prevented from destroying adrenaline. Ephedrine would thus act by a kind of substrate competition, having the same relation to adrenaline as physostigmine has to acetylcholine.

In mammals, ephedrine in suitable doses raises the blood pressure, increases cardiac activity, dilates the pupil, dilates the bronchi, inhibits the intestine and raises the blood sugar. Ephedrine does not have a marked effect on any of the body secretions. Ephedrine may stimulate the central nervous system; it has a low toxicity and is easily absorbed.

Ephedrine may be used with success in combating the fall of blood pressure in spinal anesthesia, in the treatment of bronchial asthma (bronchodilatation), hay fever, and other allergic conditions. It relieves whooping cough. Ephedrine has been used both for the prevention and the cure of attacks of heart block known as Stokes-Adam's syndrome. Use of ephedrine in the prevention of the pathological sleep of narcolepsy is now replaced by its more efficient chemical relative, deoxynorephedrine (Benzedrine). Ephedrine is of value in the treatment of myasthenia

gravis and dysmenorrhea (Chen and Schmidt; Gaddum). Ephedrine has a slight local anaesthetic action which is potentiated in cinnamylephedrine. According to Schultz and Barbour, cinnamylephedrine is ten times as potent as cocaine applied on the rabbit's cornea and twenty times as active as procaine when tested by the human intradermal wheal method (300).

Comparative investigations on the stereoisomerides of ephedrine, made by Fujii (301), Pak and Read (302), Chopra, Dikshit and Pillai (303, 304, 305), Chen, Wu and Henriksen (306) and others, showed that they have similar pharmacological effects to those of ephedrine, but differ in some particular direction and intensity of action. Compared indirectly with adrenaline, in pithed cats, *l*-ephedrine is about three times stronger than *d*-ephedrine. *l*-Ephedrine is five times as potent as *d*- ψ -ephedrine, which is seven times as potent as *l*- ψ -ephedrine (307). Pak and Read, by direct comparison in anesthetized dogs, found that *l*-ephedrine is twice as effective as *d*- ψ -ephedrine.

According to Chen, Wu, and Henriksen, norephedrine has a strong action, comparable to that of the ephedrine; nor-*d*- ψ -ephedrine has a weaker action than *l* or *dl*-ephedrine, but stronger than *d*- ψ -ephedrine.

The toxicities of ephedrine and ψ -ephedrine were compared by Fujii, who found that the latter is less toxic in frogs but more toxic in mice. Pak and Read showed that ψ -ephedrine is less toxic than ephedrine in frogs, rats, rabbits and dogs; the reverse is true in hamsters. Chen, Wu, and Henriksen found that the M. L. D. expressed in mg./kg. body weight, in white rabbits was: *l*-ephedrine 60; *dl*-ephedrine 60; *d*-ephedrine 80; *d*- ψ -ephedrine 75; *dl*- ψ -ephedrine 70; *l*- ψ -ephedrine 80; norephedrine 70. The natural tertiary amine, *l*-methylephedrine was proved to be much less active than ephedrine.

Chen (308) and later Bleyer (253) showed that synthetic ephedrine resembles in all the chemical and pharmacological properties the natural alkaloid.

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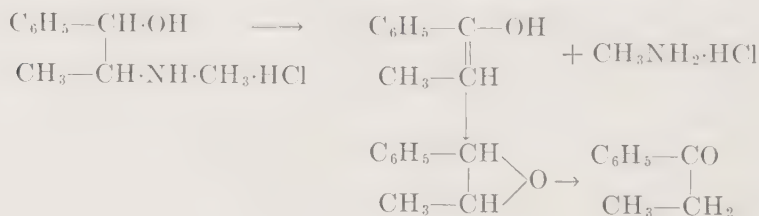
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Reaction Scheme for Hydramine Degradation (see p. 350)



CHAPTER 24

The Ipecac Alkaloids

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	Page
I. Introduction	363
II. Interrelation of the Alkaloids	364
III. Structure of the Alkaloids	366
1. Emetine	366
a. Oxidative Degradation	366
b. Nature of the Nitrogen Atoms	367
c. Early Formulas	368
d. Accepted Structure	372
2. Cephaeline, Psychotrine and <i>O</i> -Methylpsychotrine	378
3. Emetamine and Rubremetine (Dehydroemetine)	379
IV. Extraction and Industrial Preparation of the Alkaloids	382
a. Methylation of Cephaeline	383
b. The Minor Alkaloids	384
V. Color Reactions	384
VI. Table of Physical Constants	384
VII. Physiological and Therapeutical Properties	390
General References	391

I. Introduction

Ipecac root has been used in therapy since the beginning of the XVIIth century as an emetic and expectorant; its use against dysentery, already recommended by Helvetius in the eighteenth century, was found to be therapeutically correct in 1912, when emetine, the most important of its alkaloids, was successfully used by L. Rogers (80) in the treatment of amebic dysentery. This very important application has stimulated many investigations of Ipecac root and has shown emetine to be an almost indispensable alkaloid.

Two kinds of Ipecac (Fam. Rubiaceae) from which the alkaloids, and in particular emetine, can be extracted are important in commerce, namely: (a) the Ipecac of Brazil called Rio Ipecac (Mato Grosso and Minas types) supplied by *Psychotria ipecacuanha* Stokes (*Cephaelis ipecachuanha* Rich., *Uragoga ipecacuanha* Baill.) which is indigenous, and at present cultivated at the Experimental Station of Caceres (1) (Mato Grosso) as well as in the Indies and Malaya where it yields the commercial variety known as Johore Ipecac; (b) the Carthagena Ipecac *Psychotria granadensis* Benth. *Uragoga granatensis* Baill., *C. acuminata* Karsten harvested in Colombia and Venezuela and also known as Nicaragua or Panama Ipecac.

* Translated from the French of the author by R. H. F. Manske with the help of H. R. Frisch.

The use of the following related Rubiaceae has also been recommended, but their admixture with genuine root, while not an outright adulteration, is to be regarded with suspicion since the alkaloid content is variable both as to identity and quantity: *Psychotria emetica* LL. f., *Richardsonia pilosa* H. B. & K. (*R. scabra* A. St. Hil.), *R. brasiliensis* Hayne, and others (3) as *Remijia amazonica* K. Schum., *Ferdinandusa elliptica* Pohl, *Tocoyena longiflora* Aubl., *Capirona decorticans* Spruce, *Bothriospora corymbosa* Hook. f. and *Hillia tubaeiflora* Cham. (*H. illustris* K. Schum.).

Trading in Ipecac has practically become a monopoly of Brazil, and since there are many adulterations on the market it is important to use only authentic raw materials (2), with a guaranteed content of alkaloids, not less than 2%, which is demanded by most pharmacopoeas (4, 5, 6, 7, 8, 9).

The alkaloids thus far isolated from the Ipecac roots are:

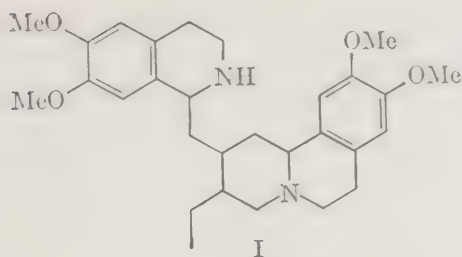
1817 Emetine	Pelletier and Magendie (10)	
1875 Emetine (pure?)	Glenard (11)	
1894 Emetine (pure!)	Paul and Cownley (12)	$C_{29}H_{40}O_4N_2$ (13, 14, 15)
1894 Cephaeline	Paul and Cownley (12)	$C_{28}H_{38}O_4N_2$ (13, 20)
1894 Psychotrine	Paul and Cownley (12)	$C_{28}H_{36}O_4N_2$
1917 O-Methylpsychotrine	Pyman (16)	$C_{29}H_{38}O_4N_2$
1917 Emetamine	Pyman (16)	$C_{29}H_{36}O_4N_2$

In 1914, Hesse (14) described two basic amorphous compounds, *ipecamine* and *hydroipecamine*, the salts of which are also amorphous, and which accompany emetine in the non-phenolic ether soluble fraction. The products were impure (16).

II. Interrelation of the Alkaloids

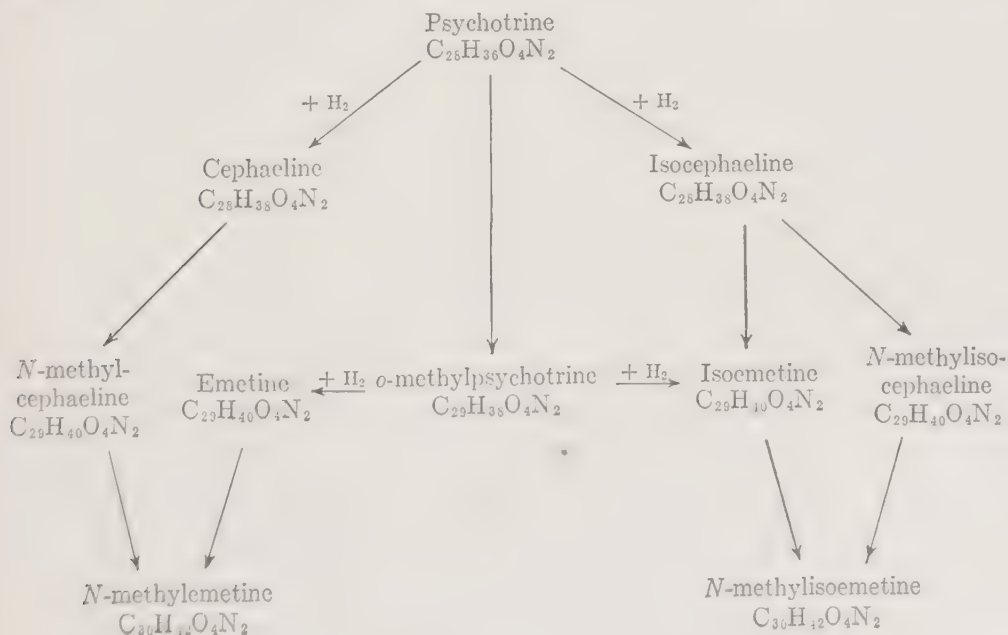
Inspection of the empirical formulas indicates a close relation between the Ipecac alkaloids which chemical study was soon to verify. Much of the early work on emetine was subsequently shown to be erroneous because the starting material was impure. The free alkaloid is amorphous but well characterized salts, especially the hydrobromide and the hydriodide, are obtainable.

The first formula for emetine, that of Dumas and Pelletier (17), was followed by many others, equally erroneous (18). Carr and Pyman (13) and Karrer (15) proposed the presently accepted formula— $C_{29}H_{40}O_4N_2$. Emetine has four methoxyls (13, 14, 15, 19), and Keller (21) has shown that one nitrogen is secondary and one tertiary, which is also the function of the nitrogens in the other alkaloids except in emetamine where they are both tertiary. In none is there an *N*-methyl group. The formula of emetine can therefore be extended to $C_{25}H_{27}N(NH)(OCH_3)_4$ and in fact the presently accepted structural formula is I.



Carr and Pyman (13) have shown that reduction of psychotrine ($C_{25}H_{26}N_2(OCH_3)_3OH$) with sodium and absolute ethanol gives rise to a mixture of cephaeline and isocephaeline by the addition of two hydrogens and when cephaeline is methylated with dimethyl sulfate and anhydrous sodium hydroxide or sodium amylate, it is mostly converted into emetine by *O*-methylation. If however, dimethyl sulphate and sodium methylate are the reagents, the major product is *N*-methylcephaeline with a little by-product *N*-methylemetine. Psychotrine can be methylated to *O*-methylpsychotrine identical with the natural base (15) and this base on sodium and alcohol reduction gives rise to a mixture of emetine and isometine (characterized by its benzoyl derivative), again by the addition of two hydrogens. In this latter reduction a third substance (base C), $C_{28}H_{38}O_3N_2$, containing only three methoxys is a by-product. It is a desmethoxyemetine or -isometine (16, 23, 24). Finally, isocephaeline on *O*-methylation gives isoemetine (23) which can be further methylated to *N*-methylisoemetine which obviously is the same as the *O*-methyl ether of *N*-methylisocephaeline.

The above interconversions are conveniently represented as follows (23):



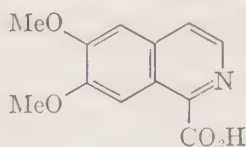
Emetamine has been obtained by Ahl and Reichstein (22) by dehydrogenation of emetine on palladized charcoal at 180–190°, in an atmosphere of nitrogen, the quantity of liberated hydrogen corresponding reasonably well to 2H_2 . The emetamine, purified as its picrate and regenerated from it, corresponds well with $\text{C}_{29}\text{H}_{36}\text{O}_4\text{N}_2$ and has the constants indicated by Brindley and Pyman (24).

Emetine and cephaeline are demethylated to the hydrochlorides of noremetine and norcephaeline (13) by heating with concentrated hydrochloric acid in a sealed tube at 135–140°. Although not crystalline these tetrahydroxy compounds are considered to be identical (emetoline) and to have the formula $\text{C}_{25}\text{H}_{32}\text{O}_4\text{N}_2 \cdot 2\text{HCl}$.

III. Structure of the Alkaloids

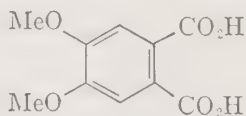
1. EMETINE

a. Oxidative Degradation. Early work on the oxidation of emetine by nitric acid by Pelletier (10) and by Podwyssotzki (31), gave only oxalic acid, or, according to Kunz-Krause (19, 32) nitrated compounds with a musk like odor. The first significant oxidation results were obtained by Carr and Pyman (13), who (in 1913), after treatment of the alkaloid with potassium permanganate in aqueous acetone, isolated a



II

small quantity of 6,7-dimethoxyisoquinoline-1-carboxylic acid (II), the decarboxylation of which yielded 6,7-dimethoxyisoquinoline, and *m*-hemipinic acid (III).



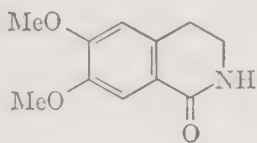
III

Windaus and Hermanns (25, 26) subsequently obtained *m*-hemipinimide by oxidizing emetine hydrochloride with potassium permanganate in aqueous solution, and Hermanns by oxidation with chromic acid isolated a product which was subsequently shown to be 4,5-dimethoxyphthalonimide.

These results indicate that emetine has at least one isoquinoline nucleus.

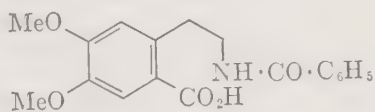
Dobbie and Fox (27) pointed out the similarity of the ultraviolet

absorption spectra of emetine and cephaeline with those of other derivatives of tetrahydroisoquinoline. Späth and Leithe (28) in 1927 confirmed the presence of an isoquinoline nucleus in emetine by potassium permanganate oxidation in slightly alkaline solution to 6,7-dimethoxy-1-keto-1,2,3,4-tetrahydroisoquinoline (IV) (corydaldine) and indicated that the



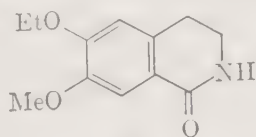
IV

linkage with the remainder of the molecule is at position 1. They also made a quantitative determination of the *m*-hemipinic acid and obtained up to 96% of theory of 1 molecule of the acid per molecule of base. Having ascertained that under identical conditions papaverine never yields more than 30 to 40% of the calculated amount of *m*-hemipinic acid, they concluded that emetine certainly contains a second group, which on oxidation also yields *m*-hemipinic acid. They therefore oxidized *N*-benzoylemetine in order to determine which nucleus gives rise to the corydaldine. The product was 3,4-dimethoxy-6- β -benzamidoethyl-benzoic acid (V).



V

Similarly the oxidation of *O*-ethyl-cephaeline (emetethyline (15) obtained by the ethylation of the free hydroxyl group) yields a mixture of 6-ethoxy-7-methoxy-1-keto-1,2,3,4-tetrahydroisoquinoline (VI) and of corydaldine, and further oxidation gave a separable mixture of 4-methoxy-5-ethoxyphthalic acid and *m*-hemipinic acid, indicating the certainty of two dimethoxy-tetrahydroisoquinoline complexes in emetine.



VI

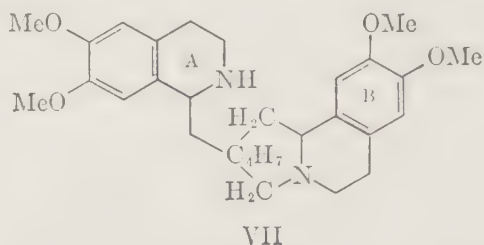
b. Nature of the Nitrogen Atoms. Complete methylation of emetine (15, 19, 20, 21, 34, 38) with methyl iodide yields a dimethiodide of *N*-methylemetine, $C_{29}H_{39}O_4N_2(CH_3)(CH_3I)_2$, which exists in two forms, α and β .*

* The complete methylation of isocemetine also yields two dimethiodides, one

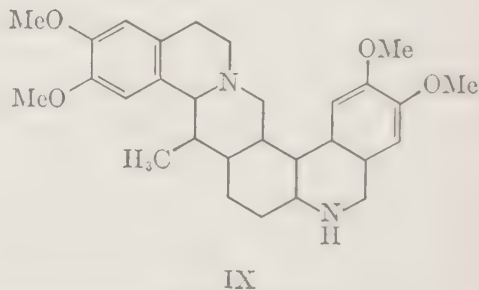
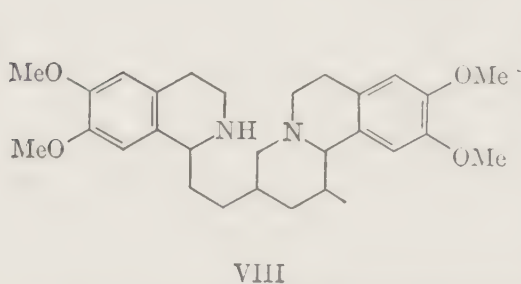
The degradation of emetine according to the Hofmann method, was first attempted by Hesse in 1914 (14), who obtained the methine as a white powder by treating the methiodide of methylemetine with silver hydroxide. Karrer (15) in 1916 succeeded in isolating the methine as its dihydrochloride. Pyman (16), however, observed that no proof of the purity of the compounds had been given and prepared the pure methyl-emetine-methine $C_{32}H_{46}O_4N_2$, the oxalate of which crystallizes well. Karrer in the meantime had shown that one of the nitrogen atoms is tertiary and is common to two rings, and that the liberation of trimethylamine at the appropriate step proved that the other nitrogen is secondary and monocyclic.

This was confirmed by Späth and Leithe (28) a dozen years later by recourse to Emde's method in which the methohydroxide was reduced with 5% sodium amalgam. Trimethylamine was eliminated at the second step of this reaction and a hydrocarbon was obtained at the third stage. The low yield (25%) of this product indicated that the tertiary nitrogen is eliminated with difficulty and that it was not the only point of union of the two isoquinoline complexes.

c. Early Formulas. Späth and Leithe on the basis of evidence available at that time (1927) proposed the partial structure VII.

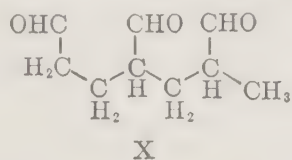


In the same year two other formulas for emetine were proposed, which are worth mentioning, one (VIII) by Brindley and Pyman (24), the other (IX) by Staub (18, 30).



being well crystallized, the other amorphous, both giving *N*-methylisoemetine-methine $C_{32}H_{44}O_4N_2$, which can be isolated as the crystalline neutral oxalate (23). This confirms the stereoisomerism of emetine and isoemetine.

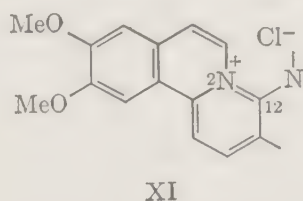
The formula of the English authors was influenced by a biogenetic hypothesis due to Robinson, according to which emetine might be derived from the condensation of two molecules of dioxyphenylalanine with 3 molecules of glyceric aldehyde. Brindley and Pyman represent the combination of the latter 3 molecules to yield 1,3,5-triformyl-*n*-hexane (X),



the terminal *C*-methyl of which would place it in such a position that the formulation of rubremetine becomes favorable (see below). The hexacyclic formula (IX) of Staub is an attempt to relate emetine with corydaline.

Formulas VIII and IX were designed to account for the formation of one of the dehydrogenation products of emetine, namely rubremetine (13) which is derived from emetine by the loss of 4H_2 . It has been obtained by Carr and Pyman as a crystalline chloride of the formula $\text{C}_{29}\text{H}_{33}\text{O}_4\text{N}_2\text{Cl}$. Rubremetine can be prepared in a yield of 35% by the action of an aqueous solution of ferric chloride at the boiling point on emetine hydrochloride. The bromide and iodide can be obtained from the chloride by treatment with the corresponding potassium halides.

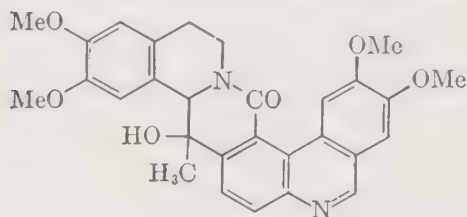
The loss of basicity of one of the nitrogen atoms in rubremetine is attributed to the formation of an "amidine" by the creation of a double bond between $\text{N}_{(2)}$ and $\text{C}_{(12)}$ in the formula of Brindley and Pyman, and these authors represent rubremetine chloride as partly shown in XI.



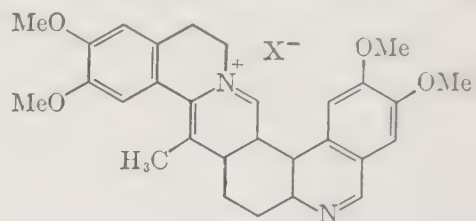
O-Methylpsychotrine, which has two hydrogen atoms less than emetine, was represented as containing a double bond between $\text{C}_{(1)}$ and $\text{C}_{(9)}$.

Karrer (15) in 1916 prepared a golden-yellow dehydrogenation product of emetine by reacting it with an alcoholic solution of iodine; this he named dehydroemetine and considered it to be different from the rubremetine of Carr and Pyman. He subsequently admitted the identity of the two compounds and gave the iodide the formula $\text{C}_{29}\text{H}_{33}\text{O}_4\text{N}_2\text{I}$, the yield by this method being of the order of 25% of theory. Pyman (16) also showed that the dehydroemetine iodide was identical with his rubremetine hydroiodide.

The uncertain state of knowledge regarding the structure of emetine at that time is well exemplified by the speculations of Staub (30) who incidentally obtained rubremetine bromide in yields of 45% by the use of bromine. Contrary to other workers (24) he regarded dehydroemetine as a separate entity and attributed to it formula XII analogous to oxyber



XII

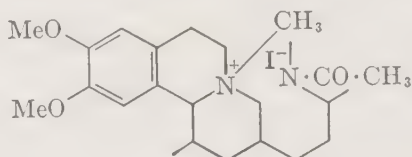


XIII

berine and reserved for rubremetine formula XIII. It should be pointed out however that there was no ambiguity regarding the empirical formula or the nature of the functional groups although the presence of two 6,7-dimethoxytetrahydroisoquinoline rings still required confirmation.

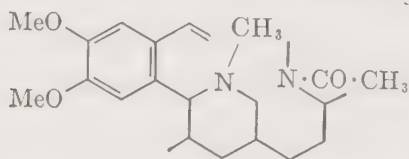
Ahl and Reichstein (22) in 1944 reported on a Hofmann degradation of *N*-acetyl-emetine, $C_{31}H_{42}O_5N_2$, which was obtained pure for the first time, in order to ascertain beyond ambiguity whether the secondary nitrogen atom belonged to a dimethoxytetrahydroisoquinoline ring. For convenience the formula of Brindley and Pyman may be used to envisage the course of the reaction.

The methiodide of *N*-acylemetine (XIV) was converted by silver oxide into the quaternary base, which, by thermal decomposition and

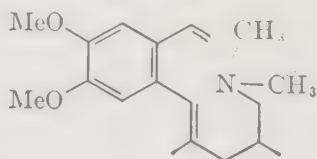


XIV

re-acetylation gave the methine base XV, $C_{32}H_{44}O_5N_2$. Retreatment of compound XV with methyl iodide and alkali led to a dimethyl-bis-des-

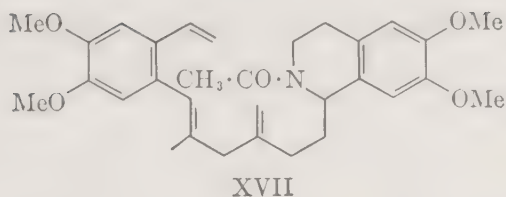


XV

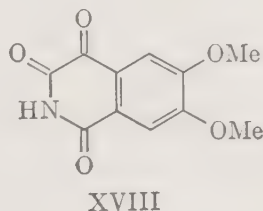


XVI

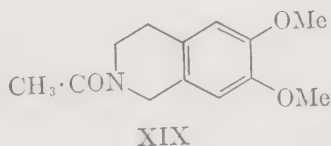
base (XVI), which still contains both nitrogen atoms. At the third degradation stage, viz. at the decomposition of the methiodide of XVI, an amorphous "neutral" product (XVII) and trimethylamine were isolated.



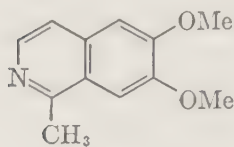
In this compound (XVII) the tertiary nitrogen atom, therefore, has been eliminated, the secondary nitrogen remaining acetylated, and its oxidative degradation should indicate the nature of the ring system containing the secondary nitrogen. Oxidation by permanganate in acetone yielded positive but not critical results since only *m*-hemipinic acid could be isolated. But if the permanganate oxidation was conducted in sulfuric acid solution, it yielded—in addition to *m*-hemipinic acid—4,5-dimethoxyphthalonamide (XVIII), $C_{11}H_9O_5N$, (a yellow crystalline compound,



already obtained by Hermanns by the chromic acid oxidation of emetine). Hence it is evident that the secondary nitrogen atom of emetine is contained in a 6,7-dimethoxytetrahydroisoquinoline ring. The structure of XVIII was confirmed by its preparation from 6,7-dimethoxytetrahydroisoquinoline or of its acetyl derivative (XIX) by chromic acid oxidation.

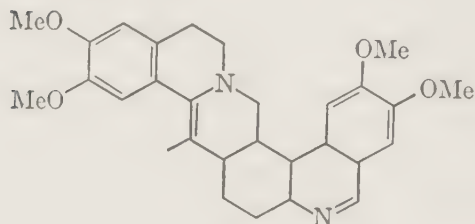


The results of catalytic dehydrogenation of emetine in the presence of palladium on charcoal at 190–200° served not to elucidate an unambiguous structure but to invalidate that of Staub. These conditions readily eliminate four hydrogen atoms from tetrahydroisoquinolines to generate isoquinolines if substituents, particularly on nitrogen, do not hinder the dehydrogenation and emetine evolves 2 moles of hydrogen to yield two crystalline bases along with amorphous material. One of these was shown to be 1-methyl-6,7-dimethoxyisoquinoline (XX) and the

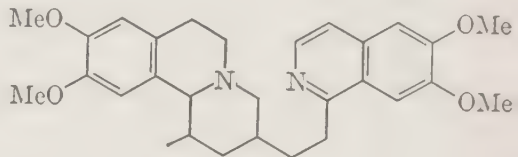


XX

other, $C_{29}H_{36}O_4N_2$, was identical with emetamine (24). It is ditertiary, has $[\alpha]_D^{20} + 11.1^\circ$ and crystallizes in two modifications melting at $135-137^\circ$ and $153-157^\circ$ respectively. The formation of XX is confirmatory evidence of the dimethoxyisoquinoline nucleus with a substituent at position-1 while the formation of emetamine disposes of the Staub formula (X) because dehydrogenation could not be expected to stop at the loss of only $2H_2$ and certainly formula XXI for emetamine was no longer tenable although the results did not exclude that of Brindley and Pyman (XXII).

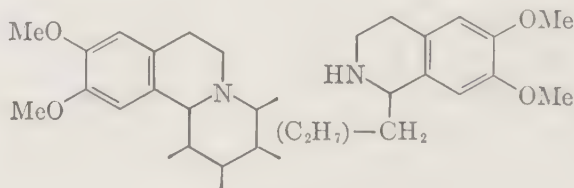


XXI



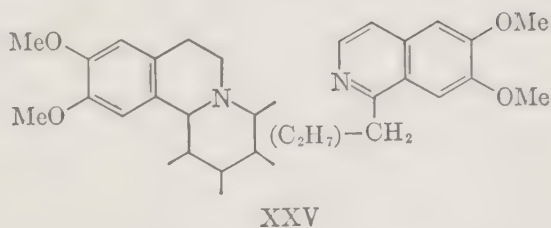
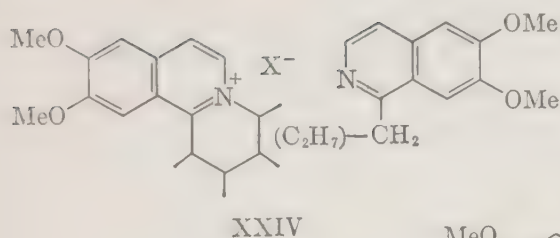
XXII

d. Accepted Structure. It is thus evident, that, while some of the structural formulas of emetine discussed above are possible, none represent the alkaloid with certainty. Karrer, Eugster, and Rüttner (33) in 1948 pointed out that even the Brindley and Pyman formula (VIII) did not adequately account for the formation of dehydroemetine in which one nitrogen is no longer basic and the other is quaternary, and which on reduction by zinc and sulfuric acid takes up only four hydrogens to generate tetrahydrodehydroemetine, and not a hexahydro-derivative as required by the older formulas. They pointed out that structure XXIII

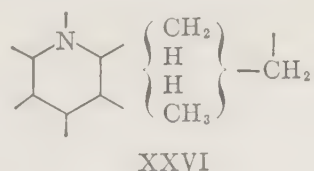


XXIII

for emetine permits of a logical interpretation of the formation of dehydroemetine (XXIV) and its reduction to its tetrahydro derivative (XXV),

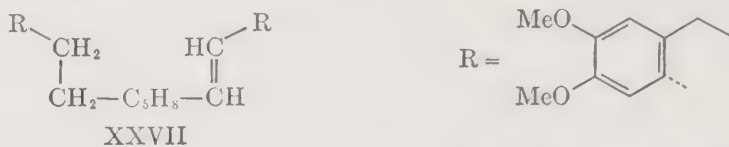


the pyridine ring in the last remaining intact under the mild conditions of the reduction. The nature of the C_2H_7 -residue was left in doubt but the presence of the methylene group at position-1 was inferred when they obtained the 1-methylisoquinoline (XX) by heating the product obtained in the third stage of the Hofmann degradation (22) of *N*-acetylemetine with zinc dust. Further proof of the presence of the methylene group in the assigned position was supplied in 1949 by Battersby and Openshaw (47) who obtained *N*-benzoylcorydaldine by the degradation of *N*-benzoyl-*O*-methylpsychotrine. The presence of one *C*-methyl was also indicated by the Kuhn-Roth method (found, 2.95, calculated, 2.7%) and the formula for emetine was accordingly extended to XXVI.

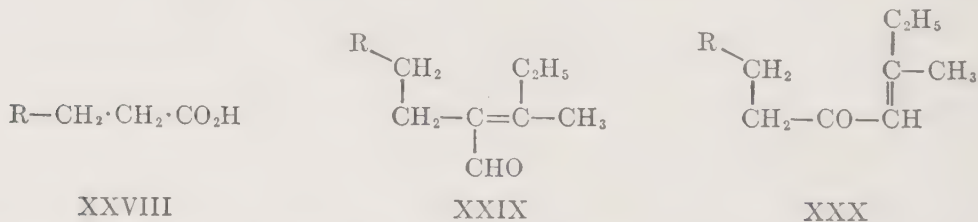


Späth and Pailer (34) in 1948 also submitted some experimental results designed to determine the nature of the bridge connecting the two isoquinoline nuclei. The dimethiodide of *N*-methylemetine was converted to its bis-methine via the hydroxide. This was hydrogenated to the corresponding tetrahydro compound and treated with methyl iodide in boiling methanol. The resulting well crystallized methiodide had been formed by the usual quaternization reaction but under the reaction conditions one molecule of trimethylamine was eliminated as its hydriodide. This elimination of nitrogen is not common but Pailer and Bilek (35) have recorded similar eliminations. That the elimination is strictly analogous to the course of the Hofmann elimination was ascertained by the fact that the resulting monomethiodide can be effectively hydrogenated in acetic acid over palladium sponge to a dihydro deriva-

tive. Furthermore the corresponding methohydroxide on appropriate treatment yielded a doubly unsaturated base and the dihydromethohydroxide generated an unsaturated base with only one double bond. The latter on further degradation ultimately gave a nitrogen free compound which is doubly unsaturated and for which structure XXVII



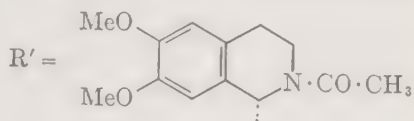
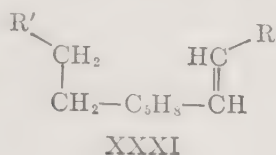
(R is 6-ethylveratryl) was given. This was based on the earlier partial formula (VII) of Späth and Leithe for emetine and the degradation is another confirmation that the tertiary nitrogen is common to two rings. The unsaturated compound (XXVII) on ozonolysis yielded 2-ethyl-4,5-dimethoxybenzoic acid along with a little 2-ethyl-4,5-dimethoxyphenol. It was pointed out that the formation of the phenol in small amounts in reactions of this kind is a general one. There was also obtained the corresponding aldehyde and a singly unsaturated carbonyl compound ($\text{C}_{18}\text{H}_{26}\text{O}_3$) which was separable as its semicarbazone. The presence of a single double bond was shown by the hydrogenation of this compound to $\text{C}_{18}\text{H}_{28}\text{O}_3$ which still formed a semicarbazone. The unsaturated compound on permanganate oxidation yielded β -(2-ethyl-4,5-dimethoxyphenyl)propionic acid (XXVIII) and its ozonolysis gave detectable amounts of methyl ethyl ketone. Two formulas (XXIX and XXX) are



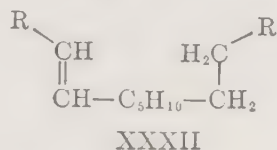
therefore possible for the unsaturated carbonyl compound—one representing it as an aldehyde and the other as a ketone. Obviously the aryl radical in these degradation products comes from ring A (VII) since it is the nitrogen of this portion that is eliminated at an early stage and since the double bonds thus formed are saturated before the ultimate elimination of the second nitrogen. There are nevertheless at least two possible representations for emetine based on formulas XXIX and XXX for the nitrogen free degradation product.

Pailer (36) repeated and extended the work of Ahl and Reichstein (22) in the Hofmann degradation of *N*-acetylemetine. The methine resulting from the first step was hydrogenated and then carried through

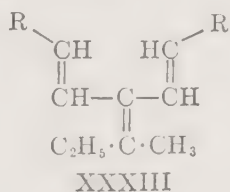
two more steps to yield a neutral *N*-acetyl compound which is doubly unsaturated and which was represented by XXXI. This substance was



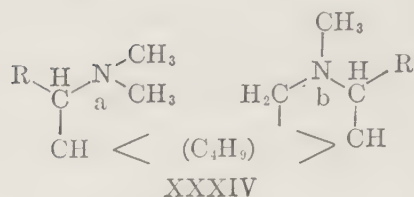
then reduced to its tetrahydro derivative, deacetylated, and again exhaustively methylated, hydrogenation being employed after the first step. The resulting neutral nitrogen free compound, which was given formula XXXII, on ozonolysis also gave rise to 2-ethyl-4,5-dimethoxy-



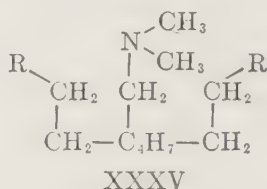
benzoic acid, the corresponding phenol and aldehyde, and a neutral carbonyl compound whose semicarbazone was identical with that obtained in the degradation of emetine itself. Furthermore, the synthesis of the dihydro derivative of XXIX was achieved by an unambiguous route involving the synthesis of a tetrahydroisoquinoline, its Hofmann degradation and hydrogenation at appropriate stages, and ozonolysis of the unsaturated ultimate intermediate (37). It is evident that the veratryl group in this carbonyl compound has its source in the one instance from ring A (VII) and in the other from ring B and therefore it must be represented by XXIX. Consequently the nitrogen free product from which it is derived must be XXXIII and this fixes the structure of the entire carbon skeleton of emetine.



Battersby and Openshaw (38) also studied the Hofmann degradation. For the greater part the earlier work of other chemists was confirmed but a number of new observations were recorded. They observed the facile elimination of trimethylamine as its hydriodide from the dimethiodide of tetrahydro-*N*-methylemetinebismethine and in model experiments Norcross and Openshaw (39) showed that dialkylbenzylamines with a methoxyl in the *p*-position also underwent this ready elimination. They concluded that their bismethine is XXXIV. Hydrogenation of double

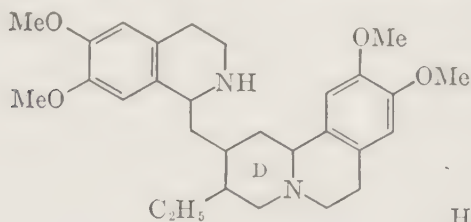


bonds was carried out at each stage of the degradation either on the Hofmann product or during Emde degradation and the penultimate des- $N_{(a)}$ - N -methylemetineoctahydrobismethine (XXXV) again methylated and decomposed to yield a neutral nitrogen free compound ($\text{C}_{25}\text{H}_{30}(\text{OCH}_3)_4$)

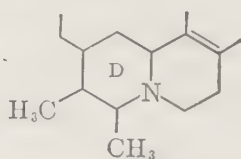


which on ozonolysis (38, 41, 47) yielded polymeric formaldehyde and a non-aldehydic carbonyl compound. Of special interest was the observation that the dimethiodide of XXXIV yields a crystalline addition compound with ethylene dichloride very sparingly soluble in that solvent and hence easily separable from the monomethiodide which is also formed if the reaction is carried out in ether at room temperature. The decomposition of the dimethiodide to the monomethiodide and trimethylamine hydriodide was conveniently achieved by heating in diethyl ketone at 100° .

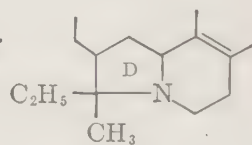
The writing of a structure based upon the above observations (40, 41) resolves itself into three possibilities (XXXVI, XXXVII, XXXVIII) and these differ only in the size and substituents of ring D.



XXXVI



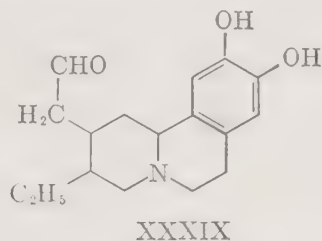
XXXVII



XXXVIII

At this point Robinson (43) adopted the biogenetic mechanism first advanced by Woodward (42) to account for the natural synthesis of a portion of the strychnine molecule. Three molecules of dihydroxyphenylalanine are required. One of the molecules is assumed to suffer scission between the hydroxyls, the 3-carbon becoming aldehydic, the

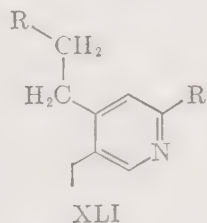
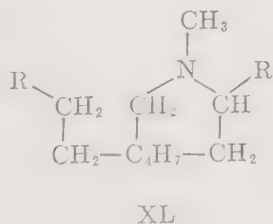
4-carbon being completely reduced. This can presumably take place before or after condensation with a second molecule as well as one of formaldehyde resulting in a compound of structure XXXIX which by



condensation with a third molecule of dihydroxyphenylalanine followed by decarboxylation and methylation would give rise (45) to XXXVI (=I) and hence should be emetine. Proof of this structure was advanced by Pailer and Porschinski (40) and by Battersby and Openshaw (46, 47).

The former authors proceeded in two ways. (a) The dibenzylidide of *N*-methylemetine on treatment with alkali effected a double ring scission to yield a product which on catalytic hydrogen absorbed 3 moles of hydrogen. Two of these were consumed in the rapid saturation of the double bonds and one in the slower hydrogenolysis of the *N*-benzyl radical to yield toluene. The unsaturated compound on thermal dehydrogenation at 300–310° in the presence of palladium generated 3-ethyl-4-methylpyridine (β -collidine). (b) *N*-Benzoylemetine was converted into its monobenzylidide and this on appropriate degradation gave a singly unsaturated methine which also could be reduced and hydrogenolyzed in one operation. This unsaturated compound also gave rise to β -collidine on appropriate thermal dehydrogenation. Structure XXXVII is definitely excluded by these results and the authors preferred XXXVI without definitely rejecting XXXVIII, because a molecular rearrangement could conceivably have resulted in the enlargement of ring D. Such ring enlargement has however not been observed under similar experimental conditions with *N*- and *C*-methylated derivatives of pyrrolidine (48).

Battersby and Openshaw dehydrogenated des-*N*_(a)-emetine-hexahydromethine (XL) in the presence of palladium at 260–270° to obtain



the crystalline pyridine derivative (XLI) which on oxidation with concentrated nitric acid gave 5-ethylpyridine-2,4-dicarboxylic acid in 40% yield, the structure of which was proved, (a) by oxidation with permanganate to pyridine-2,4,5-tricarboxylic acid (berberonic acid), and (b) by decarboxylation with soda lime to 3-ethylpyridine. The comparatively mild conditions of these experiments confirm and offer independent proof of the size of ring D and of the position of the ethyl side chain and establish without ambiguity formula XXXVI for emetine.

2. CEPHAELINE, PSYCHOTRINE AND *O*-METHYLPSYCHOTRINE

Cephaeline, the most important of the secondary alkaloids of *Ipecac*, contains three methoxyls and one phenolic hydroxyl, the methylation of which converts the base into emetine.

Psychotrine is converted into a mixture of cephaeline and isocephaeline by reduction and into *O*-methylpsychotrine by methylation.

The problem of the constitution of these 3 alkaloids is therefore reduced to the determination of the position of the phenolic hydroxyl in cephaeline (at the same point as in psychotrine), and that of the double bond in psychotrine and *O*-methylpsychotrine.

It had been previously reported that oxidation of the ethyl ether of cephaeline (or emetethyline) yields a mixture of 1-keto-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 1-keto-6-ethoxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (VI) (28), which locates the ethoxyl group in one of the rings.

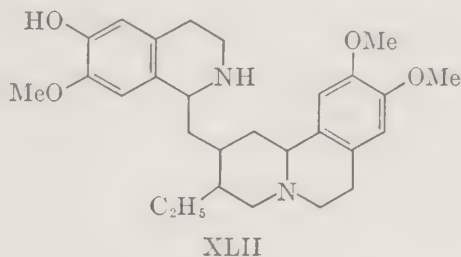
O-Methylpsychotrine can be partially hydrolyzed to regenerate psychotrine almost quantitatively, which indicates that one of the four methoxyls is unduly labile. Such lability is observed only when the methoxyl is para to a vinyl group.

Reduction of *O*-methylpsychotrine by sodium and alcohol yields a mixture of emetine and isoemetine (16), whereas with hydrogen in the presence of platinum in neutral solution, or of Raney nickel (33) isoemetine is obtained. The production of two pairs of isomers, cephaeline and isocephaeline, emetine and isoemetine, by hydrogenation of the double bond, indicates the creation of a new asymmetric center, and this limits the possible position of the double bond. Furthermore, *O*-methylpsychotrine on oxidation by bromine, iodine, or ferric chloride yields rubremetine (33).

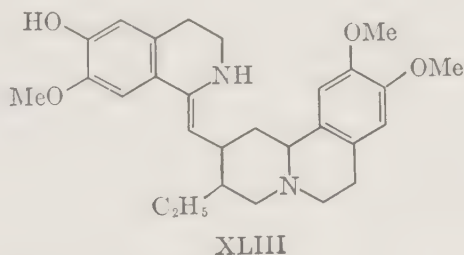
Since the formulas of Brindley and Pyman (24) for psychotrine and *O*-methylpsychotrine were based on an erroneous formula for emetine they are evidently untenable. However, Karrer, Eugster and Rüttner (33) have shown that the double bond is actually in the position assumed by the former authors, namely, in a position para to the free hydroxyl

which is in the 6-position of the isoquinoline nucleus. The oxidation of *N*-benzoyl-*O*-methylopsychotrine by perphthalic acid or by ozone yields *N*-benzoylcorydaldine and hence the double bond is extra cyclic.

Pailer and Porschinski (49) have repeated a Hofmann degradation of *O*-ethylcephaeline which proceeded in a manner entirely parallel to that of emetine (34). The ultimate methochloride on ozonolysis yielded an aldehyde whose semicarbazone melted at 181–182°. This proved to be identical with the semicarbazone of synthetic 2-ethyl-4-ethoxy-5-methoxybenzaldehyde but was different from the aldehyde in which the alkoxy

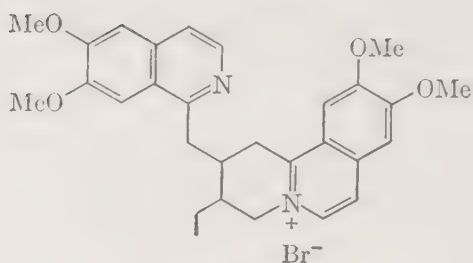


groups were reversed. Cephaeline is therefore XLII and psychotrine is XLIII. *O*-Methylopsychotrine is XLIII with a methoxyl in place of the hydroxyl.



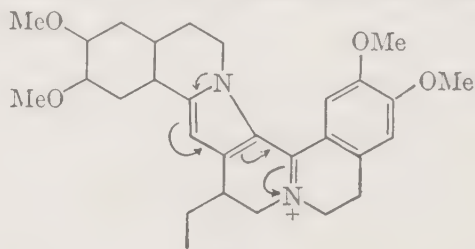
3. EMETAMINE AND RUBREMETINE (DEHYDROEMETINE)

Emetamine is $C_{29}H_{36}O_4N_2$ and rubremetine or dehydroemetine (artifact) is $C_{29}H_{32}O_4N_2$, that is, emetine having lost four and eight hydrogens respectively. Ahl and Reichstein obtained emetamine by catalytic dehydrogenation of emetine and interpreted their results on the basis of the Brindley and Pyman formula. Karrer, Eugster and Rüttner (33) preferred to indicate empirically the link between the two isoquinoline nuclei. They point out that tetrahydrodehydroemetine is not identical with emetamine although many of their reactions are closely similar and ascribe this difference to the disposition of the groups about the asymmetric carbon-1. Furthermore, catalytic dehydrogenation of emetine and emetamine do not yield the same dehydroemetine (16) (rubremetine) and this lack of identity is strikingly borne out by the



XLIV

ultraviolet spectra. They proposed a structure for rubremetinium bromide which as now interpreted would be XLIV, and which was rejected by Battersby, Openshaw, and Wood because it fails to explain (a) the loss of basicity of the non-quaternary nitrogen; (b) the intense red-orange color of the salts; (c) the non-identity of rubremetine with a similar oxidation product of emetine; and (d) catalytic reduction of rubremetine to a dihydro derivative which is easily oxidized in air (38). Moreover, although emetine hydrochloride is readily oxidized to rubremetinium chloride with mercuric acetate (45% yield) in boiling aqueous acetic acid, 1-*n*-butyl-3,4-dihydroisoquinoline remains unaltered under these conditions.* The same authors in this oxidation obtained a tetrahydroemetine ($C_{29}H_{36}O_4N_2$) containing two double bonds which is isomeric or possibly identical with tetrahydrodehydroemetine. It was isolated as its acid oxalate. On the basis of their observations and those

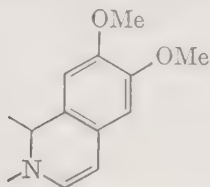


XLV

of others, the English authors propose structure XLV for rubremetine. This bears a close relation to the cyanine dyes which are resonance hybrids and thus highly colored compounds. The formula explains the fact that rubremetine can be reduced only to a tetrahydro derivative with zinc in sulfuric acid. The latter (XLV) is a pyrrole derivative and as such not susceptible to facile reduction and gives the red pine splinter test and the deep blue-green color with Ehrlich's reagent. Karrer and Rüttner (50) however rejected this formulation on the basis that a compound such as XLV should readily lose more hydrogen because of the two ortho-dihydropyridine nuclei in the molecule. They point out furthermore that, since lithium aluminum hydride reduces cyclic quater-

* Recently reinvestigated by Hazlett and McEwen (101) and by Openshaw and Wood (102).

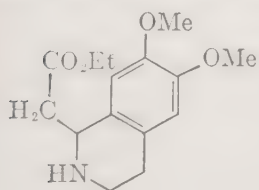
nary bases (51) to ortho-dihydro derivatives, the dihydro reduction



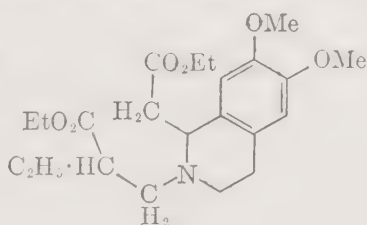
XLVI

product of rubremetinium bromide with this reagent can be represented as a dihydroisoquinoline (XLVI). In support of this argument they reduced XLVI catalytically to a dihydro base which was identical with tetrahydrodehydroemetine (m.p. 134° ; $[\alpha]_D + 42^{\circ}$ in ethanol). A small amount of an isomeric tetrahydro dehydroemetine (m.p. 194° ; $[\alpha]_D^{18} - 380^{\circ}$ in ethanol) was also obtained. These authors however failed to offer a satisfactory complete structure for rubremetine. To the reviewer it would appear as though the objections of Karrer and Rüttner are not well founded. Certainly, their reduction experiments are satisfactorily explicable on the basis of XLV, and their objection to it on the grounds of stability to oxidation is met by the resonance formula which requires no other condition of stability.

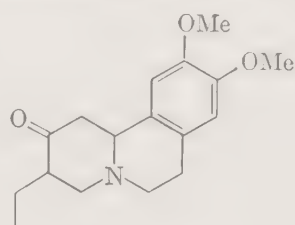
However, Battersby and Openshaw (52) supplied proof of the nuclear structure of these alkaloids in a total synthesis of *dl*-rubremetinium bromide, although the synthesis did not fix the double bonds in unambiguous positions. The half ester chloride of malonic acid was condensed with 3,4-dimethoxyphenethylamine, the amide cyclized with phosphorus pentoxide, and the derived dihydroisoquinoline reduced to XLVII. The latter was condensed with ethyl α -aldehydbutyrate and the mixture reduced to XLVIII, which by Dieckmann condensation



XLVII

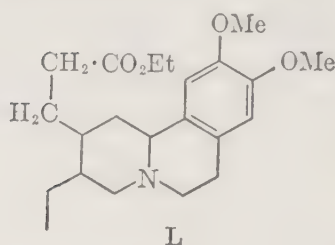


XLVIII

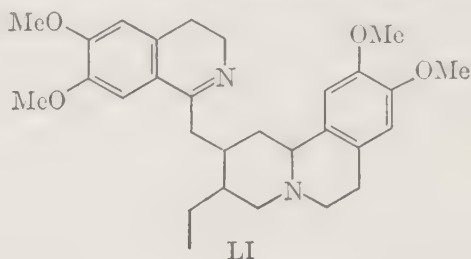


XLIX

followed by hydrolysis gave the ketone XLIX. This last on condensation with ethyl cyanoacetate in the presence of ammonium acetate, followed by hydrolysis, decarboxylation, hydrogenation, and esterification yielded L, which was condensed with a second molecule of 3,4-dimethoxyphenethylamine and cyclized with phosphorus oxychloride. The resulting crude base, isolated by distillation must be LI, that is, a mixture of



the stereoisomers of *O*-methylpsychotrine. In any case, it was oxidized with mercuric acetate to yield *dl*-rubremetinium bromide (m.p. 180–5°),



a result which amply confirms synthetically what has been so laboriously gleaned from the analytical work on the emetine alkaloids. The absorption spectra of the synthetic and derived bromides were superimposable.

It can therefore be concluded that the structures of emetine, of psychotrine, and of *O*-methylpsychotrine have been entirely determined. There remains some question as to the exact location of the double bonds in rubremetine and more serious doubt as to the structure of emetamine.*

IV. Extraction and Industrial Preparation of the Alkaloids

The roots of Rio Ipecac always contain more than 2% of total alkaloids. Carr and Pyman (13) reported 2.7% total alkaloids from which they obtained 1.35% pure emetine and 0.25% cephaeline. The following table is borrowed from Hesse (14).

Alkaloids %	Minas		Mato Grosso	Johore	Carthagena	
	a	b			a	b
Emetine	1.31	1.00	1.62	1.03	0.61	1.13
Ipecamine*	} 0.53	0.36	0.53	0.25	0.22	0.32
Hydroipecamine*						
Cephaeline	0.60	0.62	0.52	0.46	0.74	0.81
Psychotrine	0.06	0.05	0.06	0.04	0.05	0.06
Total	2.50	2.03	2.73	1.78	1.62	2.32

* Alkaloids at present not admitted.

Numerous recent analyses of Rio roots (Mato Grosso) indicate at least 2.5% total alkaloids which are roughly distributed as follows:

* Note added in proof, see page 394.

emetine, 1.5–1.7; cephaeline, 0.6–0.7; psychotrine, 0.04–0.06%. Emetamine and *O*-methylpsychotrine are present to the extent of 0.015–0.033 and 0.002–0.006% respectively (16). The alkaloids of Carthagena roots consist of 40–42% emetine, 55–57% cephaeline, and 1–3% of psychotrine. Although cephaeline is not important medicinally it can be methylated to the valuable emetine and therefore its content in the drug is of importance. The Indian drug contains about 2% of total alkaloids of which 1.2–1.3% is emetine (53) but roots younger than 4 years contain less and are not acceptable in the pharmacopoeas. The identification and falsification have been given some attention (2, 54). The pharmacopoeas give assay methods, the Swedish one requiring a minimum of 2.3% alkaloids of which 75% must be emetine. Analytical methods have been discussed in considerable detail (55–62).

The commercial isolation of the alkaloids differs in no essential feature from that employed for other alkaloids. Owing, however, to the toxic nature of the roots, all handling and grinding operations must be conducted so that the eyes, the respiratory tract, and the hands of the operators are protected. The dusts produce severe conjunctivitis, asthma, and painful inflammations at the base of the finger nails. There is also some evidence of the acquisition of hypersensibility.

Since the alkaloids are localized in the bark, and particularly in the peripheral cells under the cortex (63) pulverization can be stopped after three-quarters of the weight has been screened out (6). The high starch content of the roots may cause the formation of difficultly manageable pastes if water is used (64) in the extraction so that ethanol at 70° or methanol at 60° are the solvents of choice. The isolation of the alkaloids from the extract follows conventional methods, ether, chloroform, diisopropyl ether, or methylisobutyl ketone (65) having been used to extract the liberated bases. The phenolic bases are removed by extracting the solutions of the mixed bases with dilute potassium hydroxide solution. The non-phenolic bases are then removed by extraction with dilute sulfuric acid and the emetine then recovered as its hydrobromide or hydriodide by adding the appropriate halide to the neutralized solution. These halides are then converted to the hydrochloride by neutralizing the regenerated free base.

a. Methylation of Cephaeline. Since many methylating agents, such as methyl sulphate, also methylate the nitrogen atoms the yields of emetine from cephaeline by the use of these reagents is low.

According to a French patent (655,312) cephaeline can be *O*-methylated without effecting *N*-methylation by heating it at 130–140° with phenyltrimethylammonium hydroxide. The reaction mixture is made faintly acid and the generated dimethylaniline extracted with petroleum

ether. Strong basification with fixed alkali and ether extraction serve to isolate the emetine which can be obtained in 96% yield. With commercial cephaeline as starting material the yield is never more than 80% (personal observation).

Methylation can also be readily effected by means of nitrosomethylurethane in good yield and there are a number of patents regarding the conversion (66).

b. The Minor Alkaloids. Emetamine and *O*-methylpsychotrine remain in the mother liquors from the preparation of emetine. They may be separated by fractional crystallization of their acid oxalates or by reacting with succinic anhydride. The latter yields the half amide of succinic acid with this reagent and in this form is soluble in alkali and saponifiable by hot alkali. The insoluble emetamine is then separately purified as its acid oxalate.

V. Color Reactions

When a trace of emetine or psychotrine is dissolved in the sulfuric-molybdic acid reagent, the colorless solution soon becomes green (14); cephaeline turns the solution instantaneously into brownish red, which changes into a dirty green. *O*-Methylpsychotrine and emetamine give an emerald-green color (16). The sulfovanadic reagent gives approximately the same colored solutions.

Calcium chloride in hydrochloric acid gives a deep yellow color with emetine and with cephaeline (14).

The phenolic alkaloids cephaeline and psychotrine couple with *p*-nitrophenyldiazonium salts in alkaline solution to give purple dye-stuffs (67), the absorption spectra of which are characteristic (68). Emetamine, because of its ditertiary nature does not form such a compound, contrary to the prior opinion of Palkin and Wales (68, 69).

VI. Table of Physical Constants

The table of constants of the alkaloids begins with emetine and the more important of its derivatives, including rubremetine (or dehydroemetine). The constants of cephaeline, emetamine, psychotrine and *O*-methylpsychotrine follow. Some characteristic degradation compounds have been added.

The melting point in parenthesis is the temperature at which sintering is observed on comparatively slow heating. The abbreviations *c* and *d* signify respectively: corrected melting points and with decomposition. The letter *c* in the column $[\alpha]_D$ represents concentration, and an asterisk indicates that the reported value is calculated for the anhydrous product. The Roman figures correspond to those in the text.

TABLE I
 THE PHYSICAL CONSTANTS OF EMETINE AND ITS DERIVATIVES

Compound	M.p. °C.	$[\alpha]_D$	Crystal form	References
Emetine $C_{28}H_{40}O_4N_2$	74	-25.8° to -32.7° (ethanol at 50°, c 1.8 to 4.11) -50° ($CHCl_3$)	Amorphous	13, 15
Hydrobromide $B \cdot 2HBr \cdot 4H_2O$	(245) 250-260	+12.1 to +15.2°* (H_2O)	Needles	13
Hydrochloride $B \cdot 2HCl \cdot 7H_2O$	(235°) 255 <i>d</i>	+11.2 to +20.9°* (H_2O c 0.93 to 8.08)	Needles	13, 64, 70
$3 \cdot 5H_2O$		+53°* ($CHCl_3$)		13
		+59.9°*		71
		+37° (methanol)		70
		+53° (methanol)		70
		+51° (butanol)		70
		+44.3° (isopentanol)		70
		+17° (benzyl alcohol)		70
		+83° ($CHBr_3$)		70
Hydrofluoride $B \cdot HF \cdot 4H_2O$		+6.5° (H_2O)	Prisms	72
Iodide $B \cdot 2HI \cdot 3H_2O$	(230) 235-238		Needles	13
Nitrate $B \cdot 2HNO_3 \cdot 3H_2O$	(188)-245		Rosettes, Needles	13
Platinichloride $B \cdot H_2PtCl_6$	(253)-265 <i>d</i> 248-249		Amorphous	13 15
Sulfate $B \cdot H_2SO_4 \cdot 7H_2O$	(205)-245	+10° (H_2O)	Needles	13
Ethylemetine (Emetethyline)	68-71			15
Iodide	209-210			15
Propylemetine	58-60			15
Iodide	202-205			15
Nor-emetine Hydrochloride $C_{28}H_{32}O_4N_2 \cdot 2HCl$	240 <i>d</i>		Amorphous	13
<i>N</i> -Acetylemetine $C_{31}H_{42}O_5N_2$	97-99		Amorphous	22
Methiodide $C_{32}H_{45}O_5N_2I$	213-216		Needles	22, 36
Methochloride	192-195		Amorphous	22
Methoplatinichloride	213-217			22
Aurichloride	127-129			22
<i>N</i> -Benzoylemetine $C_{36}H_{44}O_5N_2$	185-186 <i>c</i>		Prismatic needles	13, 28, 49
<i>N</i> -Methylemetine $C_{30}H_{42}O_4N_2$		-53° ($CHCl_3$)	Amorphous	16
Hydrobromide $B \cdot 2HBr \cdot 3H_2O$	(210)-230 <i>c</i>	+6° (H_2O)	Prismatic needles	13, 16
Iodide $B \cdot 2HI \cdot H_2O$	(200) 210-220			13

* In neutral alcohol free chloroform.

TABLE 1 (Continued)

Compound	M.p. °C.	$[\alpha]_D$	Crystal form	References
Methiodide				
$\alpha(3-4H_2O)$	225-226	$-10^\circ (H_2O)$	Prisms	23
$\beta(2.5H_2O)$	262	$+68.1^\circ (H_2O)$	Tablets	23
Sulfate				
$B \cdot H_2SO_4 \cdot 5H_2O$	(210)-217 <i>c</i>	$+7.7^\circ (H_2O)$	Needles	16
<i>N</i> -Methylemetinemethine				
Hydrochloride				
$C_{32}H_{46}O_4N_2 \cdot 2HCl \cdot H_2O$	236		Square tablets	23
Oxalate	82-83	-24.6°	Prisms	16, 23
Bisbenzylidide				
$C_{44}H_{36}O_4N_2I_2$	178-179			40
Dimethiodide				
$C_{34}H_{52}O_4N_2I_2 \cdot 2H_2O$	151-153		Colorless prisms	47
<i>N</i> -Methylemetine-				
tetrahydromethine				
Perchlorate	185-186	60.2° (acetone)	Needles	38
Dimethiodide	139-140		Rhombs	38
Des- <i>N</i> (a)-emetine-				
tetrahydromethine				
Methiodide	233		Prisms	38
Methochloride	147.5-148		Tablets	38
Des- <i>N</i> (a)-emetine-				
hexahydromethine				
Methiodide $\cdot H_2O$	170-171			38, 47
Des- <i>N</i> (a)-emetine-				
hexahydrobismethine				
Picrate	159-160		Yellow needles	47
Rubremetine				
(Dehydroemetine)				
Chloride				
$C_{29}H_{33}O_4N_2Cl \cdot 6H_2O$	127-128 (air dried)		Golden yellow needles	13
Bromide				
$C_{29}H_{33}O_4N_2Br \cdot 6H_2O$	115-120 (dry)		Scarlet needles	13
Methiodide	185-187-199		Red needles	30, 33
Iodide				
$C_{29}H_{33}O_4N_2I \cdot 5H_2O$	177 (dried at 100°)		Red needles	13, 15, 30
Tetrahydro-				
dehydroemetine				
$C_{29}H_{36}O_4N_2$	134	$+41.5^\circ$ (ethanol)	Crist.	33, 50
Monomethiodide				
$C_{30}H_{39}O_4N_2I$	(145)-165			33
Dihydro-dehydroemetine				
$C_{29}H_{34}O_4N_2$	157-158	$+38^\circ$ (ethanol)	Yellow prisms	50
Isotetrahydro-				
dehydroemetine				
$C_{29}H_{36}O_4N_2$	194	-380° (?) (ethanol)		50
Tetrahydro-				
dehydroemetine				
Acid oxalate	151-153	$+84.5^\circ (H_2O)$		38
Isoemetine				
$C_{29}H_{40}O_4N_2 \cdot H_2O$	(92) 97-98	$-47.4^\circ (CHCl_3)$	Needles	23, 33

TABLE 1 (Continued)

Compound	M.p. °C.	$[\alpha]_D$	Crystal form	References
ISOEMETINE				
Hydrochloride B·2HCl	310 <i>c</i>	+12.7 to -15.6° (?) H ₂ O, <i>c</i> 0.9 to 15.07	Needles	23
Hydrobromide B·2HBr·4H ₂ O	(215) 220 <i>c</i>	+6.5 to +10.5 (H ₂ O)	Prisms	23
Acid Oxalate B·2C ₂ O ₄ H ₂ ·5H ₂ O	92-95 <i>c</i> 175-180	+1.6 to +11.3° (H ₂ O, <i>c</i> 0.8 to 1.4)	Prisms	23
Benzoyl- C ₃₆ H ₄₄ O ₆ N ₂	207-208	+48.9° (CHCl ₃)	Prismatic needles	16, 23, 24
N-Methylisoemetine C ₃₀ H ₄₂ O ₄ N ₂	152-153 <i>c</i>	-50° (CHCl ₃)	Square tablets	23
Methiodide B·CH ₃ I·H ₂ O	290-292 <i>c</i>	+92.6° (H ₂ O)	Oblong prisms	23
CEPHAELINE				
Cephaeline C ₂₈ H ₃₈ O ₄ N ₂	(106) 115-116 120-130 (dried at 100)	-43.4°* (CHCl ₃)	Needles	13
Hydrobromide B·2HBr·7H ₂ O	(266)-293		Prisms	13
Hydrochloride B·2HCl·7H ₂ O	(245)-270	+25 to +29.5° (H ₂ O, <i>c</i> 1.68 to 6.7)	Prisms	13
B·2HCl·5H ₂ O	84-86		Needles	13
Hydriodide			Oil	13
Sulfate B·H ₂ SO ₄	230-235		Amorphous	13
N-Methyl-cephaeline C ₂₉ H ₄₀ O ₄ N ₂	194-195 <i>c</i>	-48.7 (CHCl ₃)	Tablets	13
Hydrobromide B·2HBr·1.5H ₂ O	220-230 <i>c</i>	+26.5 to +29.9° (H ₂ O)	Rectangular tablets	13
Hydriodide B·2HI·1.5H ₂ O	215-235		Rectangular tablets	13
Nitrate B·2HNO ₃ ·2H ₂ O	(175) -210 <i>d, c</i>		Rectangular tablets	13
Isocephaeline C ₂₈ H ₃₈ O ₄ N ₂	(155) 159-160	-71.8° (CHCl ₃)	Plates	13
N-Methyl-isocephaeline C ₂₉ H ₄₀ O ₄ N ₂	196-197 <i>c</i>	-73.7° (CHCl ₃)	Prisms	13
EMETAMINE				
Emetamine C ₂₉ H ₄₀ O ₄ N ₂	155-156	13.6° (ethanol) 11.2° (CHCl ₃)	Needles	16, 22, 24
+0.5Et ₂ O	138-139 142-143			16, 22
Hydrobromide B·2HBr·7H ₂ O	210-225	-22 to -24.3° (H ₂ O) (<i>c</i> 4.15 to 8.04)	Shining needles	16

TABLE 1 (Continued)

Compound	M.p. °C.	$[\alpha]_D$	Crystal form	References
EMETAMINE				
Hydrochloride B·2HCl·8.5H ₂ O	77-80 218-223 (anhydrous)	-17.5° (H ₂ O)	Shining needles	24
Hydriodide	(208)-274		Needles	24
Nitrate B·2HNO ₃ ·2H ₂ O	165-166		Prismatic needles	24
Acid oxalate B·2C ₂ H ₄ O ₂ ·3H ₂ O	(165) 172 <i>d</i>	-6.1° (H ₂ O)	Needles	16, 33
Picrate	(147) 173		Needles	24
PSYCHOTRINE				
Psychotrine C ₂₈ H ₃₆ O ₄ N ₂ ·4H ₂ O	(120)-138		Yellow prisms	13
Hydriodide B·2HI	(200)-222 <i>d, c</i>		Yellow needles	13
Nitrate B·2HNO ₃ ·H ₂ O	(165) 184-187 <i>c</i>		Colorless needles	13
Acid oxalate	(130) 145 <i>d</i>		Colorless needles	13
Sulfate B·H ₂ SO ₄ ·3H ₂ O	(207)-214-217 <i>c</i>	+39° (H ₂ O)	Yellow prisms	13
O-METHYLPSYCHOTRINE				
O-Methylpsychotrine C ₂₉ H ₃₈ O ₄ N ₂	123-124	+43.2° (ethanol)	Prisms	16, 24
Hydrobromide B·2HBr·4H ₂ O	190-200	+48° (H ₂ O)	Yellow needles	16
Acid oxalate B·2C ₂ H ₂ O ₄ ·3.5H ₂ O	150-162 <i>d</i>	+45.9°* (H ₂ O)	Needles	16
Picrate	142-175		Octagonal tablets	24
Sulfate B·H ₂ SO ₄ ·7H ₂ O	247 <i>d</i>	+54.1° (H ₂ O)	Triboluminescent prisms	16
N-Benzoyl-				
C ₃₆ H ₄₂ O ₅ N ₂ ·Et ₂ O	78-80 <i>c</i> 99-100	+36.6° (CHCl ₃) +28.7° (ethanol)	Hexagonal plates	16 33
C ₃₆ H ₄₂ O ₅ N ₂ ·C ₆ H ₆	(120)-135 <i>c</i>	+36.6° (CHCl ₃) (air dried)	Hexagonal plates	16

TABLE 2
DEGRADATION PRODUCTS

Compound	M.p., °C.	References
Semicarbazone of XXIX $C_{19}H_{29}O_3N_3$	156-157	34
3,4-Dimethoxy-6-ethylbenzaldehyde Semicarbazone $C_{12}H_{17}O_3N_3$	201-202	34, 36
4-Ethoxy-5-methoxy-2-ethylbenzaldehyde Semicarbazone $C_{13}H_{19}O_3N_3$	183-185	49
2-Ethyl-4,5-dimethoxy phenol Benzoate $C_{17}H_{18}O_4$	88-90	34
β -(3,4-Dimethoxy-6-ethyl)phenylpropionic acid $C_{13}H_{18}O_4$	64-65	34
1-Methyl-6,7-dimethoxyisoquinoline $C_{12}H_{13}O_2N$	106-107	22
Corydaldine (1-Keto-1,2,3,4-tetrahydro-6,7- dimethoxyisoquinoline)	175	28
Gold salt	194	28
Mercurichloride	176	28
4,5-Dimethoxyphthalonimide	269-275 <i>d</i>	28
3-Ethyl-4-methylpyridine (β -collidine) Picrate $C_{14}H_{14}O_7N_2$	149-151	40
Styphnate	152-154	40

TABLE 3

ULTRAVIOLET SPECTRA

Emetine: Base in solution of absolute alcohol ($c = 0.3 \times 10^{-5}M$) max. λ 226m μ ; log ϵ 4.27; max. λ 283m μ ; log ϵ 3.93; min. λ 256m μ ; log ϵ 3.69 (73).

For 10^{-2} to $10^{-5}M$ solutions in ethanol P. Bayard (74) found: max. λ 283.5m μ log ϵ 3.76, and max. λ 349.5m μ ; log ϵ 1.96.

The ultraviolet spectrum of the hydrochloride or hydrobromide in aqueous solution shows a slight displacement towards the lesser wave lengths. Variations of pH lead to important modifications in the position and intensity of the λ 343m μ band; band λ 282m μ is not displaced (27).

Compound	λ max.	ϵ
<i>N</i> -Methylemetinedimethiodide (β) (38)	284	6.35
Des- <i>N</i> _(a) -emetinehexahydromethinemethiodide	286	6.80
Base XXXV	285	6.27
Des- <i>N</i> _(a) -emetinetetrahydromethinemethiodide	266	15.90
inflection	303	7.24
Des- <i>N</i> _(a) -emetinhexahydrobismethine (47)	265	12.60
inflection	303	3.56
Tetrahydrodehydroemetine (101)	245	25.60
Isotetrahydrodehydroemetine (50)	307	14.90
Tetradehydroemetine (acid oxalate) (38)	358	14.70
Dehydroemetiniumbromide (33)		
Dehydro- <i>O</i> -methylpsychotrine (bromide) (33)		
Dehydroemetamine (bromide) (33)		
<i>dl</i> -Rubremetinium bromide, synthetic (52)		
α -Dihydorubremetine (102)		
β -Dihydorubremetine (102)		
<i>O</i> -Methylpsychotrine hydrogen oxalate (103)		

VII. Physiological and Therapeutical Properties

Emetine is emetic in oral doses of 10 to 20 mg.; at higher dosage it depresses the heart and produces dilation of the coronary vessels, hence the suggestion that it be used in the treatment of angina pectoris (75). The emetic action is preserved by injection (chlorohydrate with dogs) even with simultaneous intravenous injection of procaine (76). It exerts a paralytic action on non-striated muscles and especially on the intestines (77), and is much more toxic by intravenous than by subcutaneous action (78). It is rather slowly eliminated from the organism and may accumulate. The toxic dose for man by accumulation is between 1.1 g. and 1.80 g. The lethal dose in mice is 30 mg./kg. (79).

The specific action against pathogenic ameba in human amebic dysentery makes it a valuable drug; it was introduced by L. Rogers (80) in 1912 for this purpose, and afterwards in the treatment of amebic hepatitis (81).

Dobell and Laidlaw (82) studied the action of the Ipecac alkaloids on various ameba (*Entamoeba dysenteriae*, *E. coli*, *E. gingivalis*, *Endolimax nana*) and showed that it is a hundred times as toxic to *E. dysenteriae* than it is to *E. coli*.

Laidlaw, Dobell, and Bishop (83) showed in 1928, that, working with cultures *in vitro*, all ameba are killed within 4 days in a solution of 1 part per 5 million, the pH conditions of the medium being of great importance (84, 85, 86).

After a comparative investigation of the Ipecac alkaloids and some of their derivatives, Dale and Dobell (87) concluded that emetine acts through the host rather than on the parasite, that is, changes in the blood render it amebicidal (88, 89). Satisfactory cultural methods *in vitro*, which permit pharmacological investigations (90–93) and clinical tests (94, 95, 96), have been devised.

Emetine is almost exclusively used as hydrochloride by hypodermic or intramuscular injections (0.06 g. to 0.1 g. in 24 hours in two doses). Treatment is continued for about one week with two weeks rest. Intravenous injections (with atropine) have also been recommended. It is important to interrupt the treatment after the first signs of intolerance because marked debility often results.

The camphorsulfonate and the G-penicillate of emetine (97), have also been recommended; the iodobismuthate is described in the Ph.B. for oral application in the form of gelatine capsules, as well as the periodate (schistosomiasis) and the *N*-oxide. Enteric tablets of emetine have been recommended as well for oral use (98) and a number of combinations have been used experimentally (99, 100).

Finally much work has been done with the aim of obtaining active compounds against amebic dysentery and other intestinal or hepatic parasites, the structure of which had been inspired by that of the Ipecac alkaloids (104, 105, 106).

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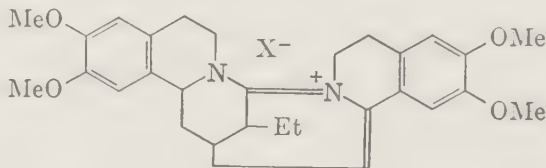
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NOTE ADDED IN PROOF

Similar conclusions have recently and independently been reached by R. P. Evstigneeva, R. S. Livshits, L. I. Zakharkin, M. S. Baïnova, and N. A. Preobrazhenskii (103).

The synthetic emetine gives the same characteristic reactions as the natural product and when heated, with iodine in EtOH yields rubremetine iodide, m. 178–80°, identical with the product from natural emetine.

These authors have also deduced the following configuration(?) for rubremetine. (See *C. A.*, **45**, 7577c (1951).)



AUTHOR INDEX

Numbers in parentheses are reference numbers and are included to assist in locating references where the author's name is not mentioned in the text. Numbers in italics refer to the page of the article on which the reference is listed.

A

Abildgaard, J., 32 (163), *61*
 Ablondi, F., 112 (51), 116 (51), *118*
 Ackermann, D., 202 (2), 203 (2, 10), 205 (2), *242*
 Ackermann, E., 7 (75), *59*
 Adams, R., 103 (12), 104 (12), 107 (20), 108, 109 (21), 111 (12, 20, 21), *118*, 318, 330, *334*, 353, *361*
 Adamson, D. W., 22 (126), *60*
 Ahl, A., 366, 370, 373 (22), 374, 379, 385 (22), 387 (22), 389 (22), *392*
 Ahrens, F. B., 157, *197*, 273 (1), *311*
 Ainley, A. D., 37 (181), 38 (181), *61*
 Airston, M., 344 (221), *360*
 Akabori, S., 205, 221, 236 (171), *242*, *246*, 353, *361*
 Alberti, C., 341, *358*
 Albertini, A., 37 (178), 42 (178), *61*
 Alder, K., 139, *195*
 Allan, W., 391 (88), *393*
 Allenby, O. C. W., 352 (267), *361*
 Alles, G. A., 70 (54), 83 (54), *99*
 Altnr, W., 319, *335*
 Amatsu, H., 340, *357*
 Anderson, A. R., 253 (1), 270 (1), *309*
 Anet, E., 141, 166, *199*
 Anet, F. A. L., 78, *99*
 Anliker, R., 291 (2), 298 (2), *311*
 Arauner, E., 223, 229 (172), 237 (172), *246*
 Ard, J. S., 267 (26), 268 (26), *310*
 Aretas, R., 391 (85, 86), *393*
 Arnaud, M., 50, *63*
 Arnolt, R. I., 320, 322, 323, 331, *335*, *336*
 Arreguine, V., 344 (174), *359*
 Asahina, Y., 69, 70 (10), 72 (10), 73 (10), 74 (10), 75, 76 (8, 10, 28, 33), 78 (28), *98*
 Ashley, J. N., 205, *242*
 Auld, S. J. M., 71, *98*
 Axer, B., 156, *197*

B

Babich, S. Kh., 344 (234), *360*
 Baesler, E., 340 (78), 352 (78), *357*
 Baeyer, A., 3, *58*, 76 (31, 32), *98*
 Baggesgaard-Rasmussen, H., 32 (163), *61*, 383 (58), *393*
 Bařnova, M. S., 390 (103), *394*
 Baker, B. R., 112 (51), 116 (51), *118*
 Balenovic, K., 51 (250), *63*
 Baltzly, R., 346, *361*
 Bamberger, A., 156 (205), *197*
 Barber, R., 270 (49a), 306 (49a), *312*
 Barbour, P. H., 355 (300), *362*
 Barger, G., 202 (1, 6), 203 (6b), 204 (6), 205 (6a, b), *242*, 268 (2), 269 (2), *309*, 313, 314, 318, 319, 324, 329, 330, 331, *334*, *335*, *336*
 Baronnet, R., 125 (314), 190, *199*
 Barral, E., 211 (138), *245*
 Barrelet, C. E., 340 (53), 353, *356*
 Barthel, W. F., 319, 322, *336*
 Bartholomäus, E., 134, 135 (124, 125), 142 (124, 125), *195*, *196*
 Barton, D. R. H., 297
 Battandier, J., 125 (93, 94), 126 (93, 94), 175, *194*
 Battersby, A. R., 367 (38), 373, 375, 376 (38, 41, 47), 377, 380 (38), 381, 386 (38, 47), 390 (38, 47), *392*
 Baumert, G., 124 (74), 130 (113), 131 (114-117), *194*, *195*
 Baup, 251, *309*
 Bayard, P., 390, *393*
 Bayerle, H., 323, *336*
 Beals, E. L., 353, *361*
 Beasley, J. L., 341 (127), *358*
 Beck, C., 108 (25), *118*
 Beck, W., 82, 84, 85 (42), 94 (42), 95 (42), 96 (42), *99*
 Beckel, A., 123 (49, 58, 59), 167, 176 (49), *193*, *194*
 Becker, A. G., 24 (140), *61*

- Becker, J., 24 (141), 61
 Beckurts, H., 80, 81, 83 (36-38), 84 (38),
 94 (36-38), 95 (36-38), 96 (36-38),
 97 (38), 98, 340 (38), 356
 Beesley, A. E., 385 (71), 393
 Beitter, A., 342, 359
 Bell, R. C., 252 (4), 253 (5), 258 (5), 259
 (4, 5), 264₂(4, 5), 265 (4, 5), 270 (5), 309
 Benedict, S. R., 202 (7), 204 (7), 242
 Benevolenskaya, Z. V., 142, 196
 Benington, F., 327, 338
 Benoit, E., 340 (54), 353, 356
 Benoit, G., 340 (55), 352, 356
 Berend, L., 124 (73), 131 (73), 194
 Bergel, F., 255 (6), 260 (6), 261 (6), 262
 (6), 309
 Bergerhoff, K., 167, 198
 Bergh, G. F., 123 (51, 52), 176 (52), 193
 Beri, M. L., 103 (24), 104 (24), 118
 Beringer, K., 332, 333, 337
 Berinzaghi, B., 70 (17), 74 (30), 77 (30), 98
 Bernhart, K., 12 (89), 59
 Bernheim, F., 315, 323 (8), 333, 334
 Bernheim, Mary L. C., 315, 323 (8), 333,
 334, 338
 Besendorf, H., 158, 162 (266), 169 (266),
 198
 Beyer, K. H., 330, 337, 353, 361
 Beyler, R. E., 163, 165, 174 (278), 191
 (278), 198
 Biddle, H. C., 9 (78), 59
 Biederbach, F., 210 (135), 245
 Bilek, L., 373, 392
 Bischoff, C. A., 73, 74, 98
 Bishop, A., 391, 393
 Black, O. F., 206 (89), 244, 341, 358
 Blanc, F., 391 (96), 393
 Blanc, L. G., 210 (115), 234 (115), 244
 Blanchard, K. C., 24 (144), 61
 Blanquet, L., 383 (64), 385 (64, 70), 393
 Blaschko, H., 354, 362
 Blau, H., 319, 335
 Bleyer, B., 355, 362
 Bliss, A. R., Jr., 383 (55), 392
 Bloem, F., 76 (31), 98
 Blount, B. K., 272, 273 (3), 274, 301 (3,
 4), 311
 Boicevic, K., 140 (139), 195
 Böhringer, C., 3 (29), 50 (29, 237), 58, 63,
 80, 81, 83 (35), 84, 85 (35), 94 (35),
 96 (35), 98
 Boeckelheide, V., 140 (141, 143), 141, 195
 Bönicke, K., 85 (44), 96 (44), 97 (44), 99
 Böttcher, B., 19 (106), 21 (117), 60
 Böttcher, I., 257 (48), 262 (48), 310
 Boit, H. G., 309, 391 (102), 393
 Bolland, A., 210 (131), 217 (131), 229
 (133), 241 (132), 245, 324, 336
 Bolotnikov, S. M., 210 (110), 212 (110),
 244
 Bondi, A., 124 (75), 126 (75), 194
 Bonnin, H., 391 (85, 86), 393
 Born, D., 312
 Borodina, G. M., 318, 334
 Bose, P. K., 69 (15), 71 (15), 76 (15), 90
 (56), 98, 99
 Bossert, R. G., 352, 361
 Bottazzi, P., 318, 334
 Bourcet, P., 212 (151), 245
 Boutroux, L., 50 (246), 63
 Brady, E. S., 344 (221), 360
 Braun, E., 31 (159), 61, 340, 351 (59),
 352, 356
 Braun, J. von, 11 (88), 27, 59
 Braun, W., 134 (121), 135 (121), 136 (121,
 127), 137 (127), 141 (127), 143 (127),
 158 (251), 161, 195, 198
 Bredemann, G., 270
 Bredenbergh, J. A. W., 23 (132), 60
 Bretschneider, H., 352, 361
 Breusch, F., 153 (185), 196
 Breyer-Brandwijk, Maria G., 268 (7), 309
 Briggs, L. H., 121 (20), 122 (20, 40), 124
 (40, 83, 84, 85), 125 (20, 40, 83-85),
 127 (40), 128, 144 (20, 83), 170 (20),
 178 (40, 83, 84, 190), 193, 194, 249
 (11-14), 250 (11, 12, 13), 252 (4, 8-
 13), 253 (1, 5, 14), 254 (11), 256 (15),
 258 (5, 11, 15), 259 (4, 5, 11, 15-17,
 28), 260 (15), 263 (11, 16, 17), 264
 (4, 5, 17), 265 (4, 5, 15-17), 266
 (15-17), 267 (12), 270 (1, 5), 309, 310
 Brindley, W. H., 365 (24), 366, 368, 369,
 370 (24), 372 (24), 378, 379, 387 (24),
 392
 Brink, N. G., 253 (18), 267 (18), 310
 Brockman, J. A., Jr., 112, 113 (44), 114
 (44), 115 (43, 44), 117 (43, 44), 118
 Brode, W. R., 352, 361
 Brown, D. G., 210 (106), 234 (106), 244
 Brown, E. D., 344 (166), 359
 Brown, R. F., 44 (216), 62

- Browning, E., 318, 330, 334, 353, 361
 Brownlee, G. W., 346 (246), 360
 Bruck, J., 328, 337
 Bruckner, V., 346 (252), 351 (252), 361
 Brückl, K., 351, 361
 Brunner, O., 86, 87 (45), 88 (45), 94 (45),
 95 (45), 99
 Brunner, W., 23 (131), 60
 Brunnenschweiler, P., 12 (91), 26, 60
 Brutschy, F. J., 15 (94), 29 (94), 30 (94),
 47 (94), 60
 Buchanan, D. N., 332, 338
 Buchka, K., 144 (164, 169), 146, 196
 Buchman, E. R., 44 (216), 62
 Buck, J. S., 319, 335
 Budde, H., 353, 361
 Büchi, J., 383 (59), 393
 Buelow, W., 323, 336
 Bümmling, G., 340 (22), 356
 Burger, A., 328, 338
 Burke, C., 332, 337
 Burkhardt, H., 42 (211), 62
 Burn, D., 312
 Burtles, R., 210 (48), 221, 230, 234 (48),
 237 (48), 243
 Bushill, J. H., 251 (34), 310
 Butlerow, A., 3 (39, 46), 58, 59
 Butt, E. M., 354, 362
 Byasson, M., 207, 243
- C
- Caille, E., 210 (114), 244
 Calliess, W., 340 (23, 25, 26, 27), 345 (25),
 351 (25), 353, 356
 Calman, A., 232 (177), 246
 Calmels, G., 214, 215, 217, 244
 Campbell, Barbara K., 38 (190), 62
 Campbell, K. N., 62 (190), 62
 Camus, L., 330, 337
 Canal, F., 124 (76), 131 (119), 132 (119),
 133, 158 (119), 194, 195
 Cannon, J. R., 78 (63), 99
 Capellmann, R., 325, 336
 Carboni, S., 341, 342 (140), 358
 Caronna, G., 249 (38), 251 (38), 252 (38),
 264 (38), 310
 Carr, F. H., 206 (84), 244, 364 (13), 365,
 366 (13), 369 (13), 382, 385 (13), 386
 (13), 387 (13), 388 (13), 392
 Carroll, J. J., 249 (14), 253 (5, 14), 258
 (5), 259 (5), 264 (5), 265 (5), 270 (5),
 309
 Cartland, G. F., 330 (128), 337, 353, 361
 Cassola, M., 130, 195
 Castrillón, J., 322, 324, 329, 336
 Caventou, E., 2, 3 (24), 58
 Cerkovnikov, E., 39 (194, 196), 45 (220),
 62
 Chaigneau, M., 234 (184), 246, 385 (72),
 393
 Chakravarti, S. N., 155 (190–192), 196
 Chakravarty, K. K., 70, 71 (18), 77 (18),
 98
 Chang, C. T., 353, 361
 Chang, Y., 112 (38), 118
 Chanley, J. D., 16 (96), 60
 Chastaing, P., 213 (158), 214 (156, 160),
 220 (157), 222, 224 (161), 234 (160),
 235 (161), 245, 246
 Chatin, J., 341, 358
 Chavez R, A. S., 341, 358
 Chelintsev, G. V., 228 (175), 246
 Chemnitius, F., 206 (81), 207 (23), 208,
 213, 214 (23), 234 (81), 242, 244
 Chen, A. L., 342, 349, 358
 Chen, H., 259 (49), 265 (49), 266 (49), 310
 Chen, J. L., 344 (176), 359
 Chen, K. K., 114 (47), 118, 155 (197),
 197, 340, 341, 342, 344 (177), 345
 (240), 349, 354, 355, 357, 359, 362
 Cheramy, P., 340, 357
 Cheymol, J., 390 (76), 393
 Chiarino, J. C., 211 (142), 245
 Chick, O., 50 (247), 63
 Chopra, R. N., 341, 342 (116), 343, 355,
 358, 362, 383 (53), 392
 Chou, T. C., 112 (41), 118
 Chou, T. Q., 112, 114 (45), 115 (45), 117
 (45), 118, 342, 343, 345 (165), 347
 (165), 349, 358
 Christensen, A., 2 (23), 19 (23), 58
 Christensen, B. V., 341 (129, 130), 344
 (130), 358
 Christensen, C. E., 383 (58), 392
 Christensen, O. T., 210 (125), 234 (125),
 245
 Christensen, V. A., 212 (143), 245, 344
 (228), 360
 Chu, J. H., 342, 349, 358
 Ch'un, T., 112 (38), 118
 Clapp, Mary A., 38 (190), 62

- Clark, G. W., 341 (121, 124), 358
 Claus, A., 10 (81-86), 59
 Clemo, G. R., 40, 45, 62, 121 (23), 122 (23), 124 (69), 127 (23), 135, 138 (131), 139 (130, 133), 140 (130, 136, 137), 141, 142 (153), 154 (133), 158, 159 (126), 160 (258), 161 (69), 163, 164, 167 (259), 168 (131, 258, 259), 169, 170 (68), 171 (259), 173, 188 (23), 193, 194, 195, 196, 198, 251 (19), 253 (19), 260 (19), 310
 Clewer, H. W. B., 250 (58), 253 (58), 270 (58), 310
 Close, W. J., 351, 361
 Coatney, G. R., 114 (48), 118
 Cockburn, W. F., 121 (7), 122 (7), 124 (7), 126 (7), 127 (315), 144 (7), 166 (7), 174 (315), 186 (315, 323), 187 (323), 188 (7), 192, 199
 Cohen, A., 34 (167), 61
 Coles, H. W., 340, 352, 357
 Collie, J. N., 153 (184), 171 (184), 196
 Comstock, W. J., 2 (11-14, 18, 22), 4 (12), 19 (14, 18, 22), 34 (11-14), 58
 Conrad, M., 68, 86 (4), 87 (4), 90, 98
 Cope, A. C., 37 (176), 44 (216), 61, 62
 Cortes, Gloria, 31 (156), 34 (156), 61
 Corti, U. A., 320, 335
 Cosel, H. von, 149, 195
 Couch, J. F., 121 (15, 17), 122 (44), 123 (64, 65, 91), 124 (78), 125 (78, 89, 90, 108), 126 (44, 65, 104), 127 (44, 47, 65, 78, 315), 128 (78), 129 (44, 64), 131 (78), 143 (78), 156 (44, 65), 166, 167 (65), 170 (15), 174 (315), 175 (90, 108), 176 (91, 291), 177, 186 (315), 187 (47), 190, 193, 194, 195, 198, 199
 Courtois, G., 391 (103), 393
 Couturier, R. G., 352, 361
 Cownley, A. J., 50 (240), 63, 206 (80, 88), 244, 364, 392
 Coy, H. H., 306 (27a), 311
 Craig, L. C., 253 (21), 256 (50), 258 (20, 21), 269 (50), 271 (36), 272 (36), 276, 277, 278 (14, 32, 35, 37), 279 (14, 32, 35, 37), 280 (32), 281 (14), 282 (36, 37, 38), 283 (14, 32, 37), 284 (38), 286 (38), 288 (36, 38), 291 (33), 295 (36), 296 (31), 297 (30, 31), 298 (33), 300 (30), 301 (5, 8, 9, 10, 27, 28), 302 (27-30), 304 (30), 305 (30), 306 (6, 7, 11, 13, 14), 307 (13, 14), 308 (12, 34), 310, 311
 Crawford, A. C., 318, 334
 Credner, K., 320, 336
 Cretcher, L. H., 23 (133), 60
 Crossley, F., 344 (181), 359
 Crowfoot, D., 301 (4), 311
 Cumming, W. M., 210 (106), 234 (106), 244
 Curtin, D. Y., 116 (49), 118
 Curtis, F. R., 354, 362
- ### D
- Dändliker, P., 42 (211), 62
 Dakin, H. D., 202 (7), 204 (7), 242
 Dale, H. H., 155 (196), 197, 202 (1), 242, 313, 314, 318, 324, 329, 330, 331, 334, 391, 393
 Dambergis, C., 69 (7), 76 (7), 98
 David, L., 383 (60), 393
 Davies, W., 346, 360
 Davis, L. S., 123 (55, 56), 124 (55), 167 (55), 193
 Davis, S. B., 191 (327), 199
 De, A. K., 103 (4), 104 (4), 105 (4), 117
 de Angelis, Maria, 82, 99
 Decker, H., 42, 62
 De Eds, F., 354, 362
 de Ipola, R. V., 71 (20), 98
 Delaby, R., 125 (314), 190, 199
 de Langhe, J., 69 (11), 74 (11), 77 (11), 98
 Deliwala, C. V., 270 (45), 276, 277 (45), 306 (45), 309 (45), 312
 Delluva, A. M., 315, 334
 Delphaut, J., 344 (173), 359
 Deschiens, R., 391 (90, 91), 393
 Desfosses, 251, 310
 Deulofeu, V., 69 (11), 70 (11, 17), 74 (11), 77 (11, 30), 98, 123 (50), 176 (50), 193, 313 (5), 334
 Dey, A. N., 227, 246
 Diels, O., 139, 195
 Dieterle, H., 255 (23, 24), 257 (23), 260 (23), 261 (25), 262 (25), 310
 Dietzel, R., 212 (155), 245
 Diguët, L., 332, 337
 Dikshit, B. B., 355, 362
 Dirscherl, W., 50 (234, 238), 63
 Dixon, W. E., 332, 338

Dobbie, J. J., 366, 390 (27), 392
 Dobell, C., 391, 393
 Doering, W. von E., 16 (96), 31 (156), 34 (156), 48 (233), 60, 61, 63, 140 (142), 191 (327), 195, 199
 Dománski, T., 20 (109, 113), 21 (109), 60
 Doolittle, S. P., 253 (27), 310
 Dopter, C., 391 (91), 393
 Dragendorff, O., 137 (129), 195
 Drewsen, V., 3 (37), 58
 Dryamova, N. A., 232, 243
 Du Bois, A. S., 352 (267), 361
 Ducloux, E. Herrero, 324, 336
 Dulière, W. L., 315, 316, 323 (11), 334
 Dumas, J. B., 364, 392
 Durand, P., 345 (238), 360
 Dussel, K., 10 (87), 59
 Dutt, A. T., 341, 342 (116), 343, 358, 359
 Dutt, S., 252 (8), 309

E

Eagles, B. A., 202 (7), 204 (7), 242
 Eastham, J. F., 297
 Eberhard, A., 340, 350, 351, 357
 Eberstaller, H., 80 (46), 81, 87 (46), 88 (46), 92, 96 (46), 97 (47), 99
 Eger, G. K., 345 (239), 360
 Ehrenstein, M., 377 (48), 392
 Ehrlich, F., 321, 336
 Ekkert, L., 210 (136), 245, 344 (168), 359
 Elderfield, R. C., 38 (190), 62
 Ellinger, A., 37 (175), 61
 Elming, N., 302
 Elvidge, W. F., 210 (137), 211 (137), 229 (137), 245
 Elvove, E., 212 (149), 245
 Emde, H., 340, 345 (29, 32, 39, 40, 42, 43), 347 (43), 349, 350, 351, 356, 376
 Engeland, R., 203 (14), 204 (14), 205 (14), 242
 Engler, 340
 Epstein, D., 390 (75), 393
 Escomel, E., 391 (89), 393
 Ettel, V., 345 (249), 360
 Eugster, C. H., 372, 378 (33), 379, 386 (33), 388 (33), 390 (33), 392
 Evstigneeva, R. P., 390 (103), 394
 Ewins, A. J., 147, 148 (175), 196, 202 (6), 203 (6b), 204 (6), 205 (6a, b), 242, 324, 336

F

Farkass, E., 122 (33), 193
 Farwell, O. A., 341 (94), 357
 Faudemay, P., 320, 335
 Felley, D. L., 191 (326), 199
 Feng, C. T., 341 (125), 342 (101, 105), 343, 344 (104, 178, 187), 345 (244), 346, 348, 349, 357, 358, 359, 360
 Fenton, S. W., 121 (19), 123 (19), 125 (19), 126 (19), 156 (19), 166 (19), 167 (19), 170 (19), 175, 193
 Ferreira da Silva, A. J., 211 (141), 245
 Fiedzuizsko, J., 34 (165), 61
 Fieser, L. F., 309
 Fieser, Mary, 309
 Fink, F., 318, 334
 Firmenich, R., 340 (54), 353, 356
 Fischer, E., 109, 118
 Fischer, O., 3 (43), 27, 59
 Fischl, 391 (94), 393
 Fish, V. A., 228 (175), 246
 Flaecher, F., 345 (248), 360
 Flamand, C., 37 (175), 61
 Fleissner, F., 2 (20), 19 (20), 58
 Fodor, G., 346, 351, 361
 Foerster, E., 332, 333 (166), 338
 Folkers, K., 112, 113 (46), 114 (46), 115 (46), 117 (46), 118, 253 (18), 267 (18), 310
 Fontaine, T. D., 250 (35), 253 (27, 35), 267 (26), 268 (26), 310
 Fornasir, V., 41, 62
 Forst, G., 3 (29), 50 (29, 237), 58, 63
 Foster, C. E., 385 (71), 393
 Fourment, P., 344 (183), 359
 Fourneau, E., 131, 134, 135, 136, 195, 340, 351, 352, 353, 356
 Fox, J. J., 366, 390 (27), 392
 Fox, S. W., 203 (9), 242
 Fraenkel-Conrat, H. L., 268 (2), 269 (2), 309
 Fränkel, S., 34 (166), 61
 Fraga, F., 125 (95a), 126 (95a), 175 (329, 330), 194, 199
 François, M., 210 (115), 234 (115), 244
 Frankforter, G. B., 273 (15), 311
 Freise, F. W., 364 (3), 391
 Fréon, P., 353, 361
 Frerichs, G., 80, 81, 83 (38), 84 (36, 38), 94 (38), 95 (38), 96 (38), 97 (38), 98

- Freudenberg, K., 31 (159, 160), 61, 340, 351, 352, 356, 357
 Freudenberg, W., 343, 359
 Freudweiler, R., 318, 334
 Freund, M., 22 (129), 23 (132), 60, 144 (165), 145, 146 (165, 173), 147, 151, 196, 273 (16-18), 297 (16, 17), 300 (17), 302 (18), 304 (16, 17), 305 (18), 311
 Fried, J., 274 (19), 275 (19), 276 (19), 290 (20), 292 (64), 293 (20), 296 (20), 299 (64), 306 (19, 27a), 307 (19), 311, 312
 Friedländer, P., 3, 58
 Friedman, 313
 Friedman, H. L., 37 (174), 61
 Friedmann, A., 144 (165), 145, 146 (165), 196
 Frisch, H. R., 363
 Fu, F. Y., 112 (41, 42), 114 (45), 115 (45), 118
 Fujii, M., 355, 362
 Fulde, A., 38 (186), 62
 Funck, E., 318, 334
- G**
- Gabriel, S., 108 (25), 118
 Gadamer, J., 350, 351, 361
 Gaddum, J. H., 340, 354, 357
 Gaebel, O. G., 320, 335
 Galinovsky, F., 121 (24), 123 (313), 124 (24), 140, 149, 150 (181, 188), 151 (181), 153 (186), 154, 155, 157 (188), 161 (188), 164 (277), 165 (277, 318, 319), 171, 173, 176, 177, 183 (24), 184 (24, 188), 190, 191, 193, 195, 196, 198, 199, 253
 Garrido, M. A., 344 (172), 359
 Gatti, A., 123 (50), 176 (50), 193
 Gauff, R., 147 (176), 196
 Gauhe, Adelheid, 252 (30), 267 (33), 268 (33), 310
 Gensler, W. J., 38 (190), 62
 Genvresse, P., 50 (246), 63
 Gerecs, A., 249 (62), 251 (62), 310
 Gerhard, K., 123 (66), 124 (77), 126 (77), 131 (77), 156 (77), 194
 Gerhardt, Ch., 3 (32), 58
 Germain, A., 157, 197
 Gerrad, A. W., 207, 243, 244
 Gessner, O., 390 (77), 393
 Gesto, M. Dolores V., 125 (95a), 126 (95a), 194
 Ghose, T. P., 102, 103, 104 (2), 105 (2, 3, 5), 106 (5), 109, 111 (2, 3, 5, 32), 117, 118, 341, 343, 358
 Ghosh, S., 341, 342 (117), 343, 358, 359
 Gibbs, E. M., 20 (112), 21 (112, 124), 28 (112), 60
 Gibson, C. S., 348, 361
 Gilfillan, F. A., 353, 361
 Gilg, E., 341, 344 (99), 357
 Gilham, P. T., 78 (59), 99
 Gilman-Blatt, 326
 Giovanni, I., 212 (154), 245
 Gisvold, O., 323, 336
 Githens, T. S., 344 (225), 360
 Glen, W. L., 270 (49a), 306 (49a), 312
 Glénard, A., 364, 391
 Glycart, C. K., 210 (111), 244, 344 (188, 189, 203), 359, 360
 Göddertz, A., 109, 118
 Göhring, R., 340 (68), 347 (68), 351, 357
 Goerner, P., 210 (118), 244
 Gohring, C. F., 3 (38), 58
 Gold, H., 330 (128), 337, 353, 361
 Goldberger, H., 123 (313), 190, 191 (313), 199
 Goldschmiedt, G., 319, 335
 Gonnard, P., 320, 321, 336
 Goodson, J. A., 19 (102), 60
 Goodwin, L. G., 391 (93), 393
 Gordon, S., 112 (51), 116 (51), 118
 Gossner, B., 351, 361
 Goto, R., 69 (12), 98
 Gottlieb, K. R., 212 (143), 245, 344 (227, 228), 360
 Goubau, R., 212 (148), 245
 Goutarel, R., 50, 52, 54, 63, 392
 Gouy, M., 210, 244
 Gow, P., 78 (59), 99
 Grace, G. S., 325, 334, 336
 Grafe, V., 211 (140), 245
 Graham, Boyd E., 330 (128), 337, 353, 361
 Grant, E. H., 344 (198, 207), 359
 Grant, G., 270 (49a), 306 (49a), 312
 Gray, A., 277
 Green, M. W., 234 (182), 246
 Green, Nancy, 234 (182), 246
 Greshoff, M., 66, 67 (1), 68, 98
 Grill, F., 344 (186), 359

Groff, G. W., 341 (121, 124), 358
 Gstirner, F., 344 (217), 360
 Günthard, H. H., 296 (62), 312
 Guggenheim, M., 203 (9), 242, 315, 316,
 318, 330, 334, 353, 362
 Guillaume, A., 210 (102), 244
 Gulland, J. M., 342, 358
 Gupta, M. P., 252 (8), 309
 Gurevich, H., 121 (4, 21), 122 (4), 125 (4),
 126 (4, 21), 127 (4, 21), 186 (4, 21),
 187 (4, 21), 192, 193
 Gurin, S., 315, 334
 Guřtak, E., 39 (195), 62
 Guy, J., 125 (314), 190, 199

H

Haag, H. B., 212 (152), 245
 Haagen-Smit, A. J., 322, 336
 Haensler, P., 46 (228), 63
 Haeuszler, H., 18 (100), 33 (100), 34
 (100), 60
 Hagemann, H., 391 (97), 393
 Hagen, G., 47 (230), 63
 Hagen, M., 167, 198
 Hagerty, M. J., 339, 355
 Hahn, G., 55 (257-259), 63, 325, 336
 Hahn, V., 45 (220), 62
 Halberkann, J., 38 (185), 62
 Haley, T. J., 344 (175), 359
 Hamerslag, F. E., 383 (65), 393
 Hanford, W. E., 103 (12), 104 (12), 107
 (20), 108, 109 (21), 111 (12, 20, 21),
 118
 Hanke, M. T., 319, 335
 Hansel, A., 55 (258), 63
 Hardy, E., 207, 208 (78), 209 (78), 214,
 215, 217, 244
 Harington, C. R., 205 (17), 242
 Harnack, E., 207, 213 (26), 214 (23, 26),
 220 (23), 228, 229 (25, 26), 230, 236
 (26), 242
 Harris, L. E., 341 (127), 358
 Harris, P. H., 114 (47), 118
 Harte, R. A., 344 (176), 359
 Hartung, W. H., 325, 330 (128), 337, 344
 (181), 352, 353, 359, 361
 Harvey, W. E., 256 (15), 258 (15), 259
 (15), 260 (15), 265 (15), 266 (15), 309
 Hashitani, Y., 320, 335
 Hass, H. B., 352, 361
 Havelock, E., 332, 338
 Havemann, H., 352 (263), 361
 Hayden, A. A., 341 (111), 342 (111),
 344 (111), 358
 Hazlett, R. N., 390 (101), 394
 Heath, H., 203 (14a), 205, 242
 Heffter, A., 320, 324, 325, 330, 332, 335,
 336
 Heidelberg, M., 23 (136), 24 (139), 61
 Heider, A., 318, 322, 335
 Heikel, G., 210 (112), 212 (112), 244
 Heimbach-Juhász, S., 47 (232), 63
 Helch, H., 210 (134), 245
 Heller, H., 325, 326, 336
 Hemmings, A. W., 204 (15b), 242
 Henderson, F. G., 114 (47), 118
 Henriksen, E., 355, 362
 Henry, T. A., 2 (2), 20 (112), 21 (112,
 124), 22 (128), 28 (112), 50 (243), 52,
 53 (253), 58, 60, 63, 309, 340, 357,
 391, 393
 Henze, M., 318, 334
 Hepner, F. E., 308 (23), 309 (23), 311
 Hermann, R., 255 (54), 257 (54), 260
 (54), 261 (54), 262 (54), 310
 Hermanns, L., 366, 371, 392
 Herr, M. E., 308 (24), 309 (24), 311
 Herrera, A. K., 126 (105), 195
 Herrero Ducleaux, E., 344 (191), 359
 Herschmann, O., 34 (166), 61
 Herzig, J., 214 (162), 229 (164), 230 (163,
 164), 236 (164), 246
 Hess, K., 297 (22), 304 (22), 311
 Hesse, O., 2, 3 (26), 9 (77), 19 (17, 104,
 114), 25 (77, 114), 50 (236, 241), 51,
 58, 59, 60, 63, 364 (14, 20), 367 (20),
 368 (14), 382, 384 (14), 392
 Heusser, H., 291 (2), 311
 Hey, P., 325, 337
 Heyl, F. W., 308 (23, 24), 309 (23, 24),
 311
 Hildebrandt, G., 353, 361
 Hilty, W. W., 344 (209), 360
 Hiner, L. D., 340, 341 (129, 130, 133), 344
 (130), 344 (92), 357, 358
 Hirsch, J., 353, 361
 Hoare, C. A., 391 (93), 393
 Hobschette, A., 332, 338
 Hochstätter, W., 18 (100), 33 (100), 34
 (100), 34 (168), 60, 61
 Hodgkin, J., 50 (242), 63

- Hoerlin, J., 5 (61), 59
 Höter, H., 34 (169), 61
 Hoffmann, E., 162 (269, 270), 169 (269, 270), 198
 Hoffmann, F. K., 41 (201), 62
 Hofmann, A. W. von, 35
 Hoggarth, E., 45 (223), 62
 Holmes, E. M., 206 (18-20, 88), 207 (18-21, 22), 242, 244, 341 (95), 357
 Holmes, H. L., 199
 Holschneider, F. W., 133, 136, 138, 139 (132), 140 (144, 145), 141 (120), 142 (144, 145), 143 (120, 160, 161), 159 (257), 169, 195, 196, 198
 Holtz, F., 202 (2), 242
 Holz, P., 323, 336
 Homolka, B., 76 (32), 98
 Honda, J., 69, 71 (9), 76 (9), 98
 Hoo, V., 210 (128), 234 (128), 245
 Hoogewerff, S., 3 (42, 54), 37 (42), 59
 Hooper, D., 102, 103 (1), 111 (1), 112 (40), 117, 118
 Hoover, F. W., 352, 361
 Horkheimer, P., 145, 146 (173), 151, 196
 Horowitz, S., 21 (117), 60
 Horst, P., 273 (25), 311
 Hosansky, N., 287
 Howard, B. F., 50 (247), 63
 Howard, D., 2 (2), 50 (235, 242), 58, 63
 Hsieh, C. Y., 344 (205), 360
 Hsu, Y. D., 344 (204), 360
 Huang, K. C., 112 (41, 42), 118
 Huber, M., 46 (227), 63
 Huebner, C. F., 291 (39), 292 (39), 295 (39), 298 (39), 299 (39), 311
 Hughes, G. K., 70 (19), 77 (19), 78 (58, 59, 63), 98, 99, 141, 166, 199
 Hume, A. N., 341 (132), 342 (132), 358
 Huntenberg, W., 38 (188), 47 (188), 62
 Hunter, G., 202 (8), 204 (8b, 14b), 242
 Husemann, A., 143, 196
 Hutchings, B. L., 112 (51), 116 (51), 118
 Huyck, C. L., 344 (231), 360
 Hyde, J. F., 318, 330, 334, 353, 361
- I
- Ibele, J., 12 (89), 59
 Imbesi, A., 206 (82), 244
 Indra, A., 344 (232, 233), 360
 Ing, H. R., 121 (5, 6), 122 (5, 6), 124 (5), 126 (5), 129, 148, 149, 152, 155, 156 (199), 159, 166 (6), 168, 170 (6), 171 (183), 173 (6), 192, 196, 197
 Inubuse, M., 69, 70 (10), 72 (10), 73 (10), 74 (10), 75, 76 (8, 33), 98
 Irving, G. W., Jr., 253 (27), 310
 Iselin, B. M., 290 (20), 292 (64), 293 (20), 296 (20), 299 (64), 311, 312
 Ito, Y., 177 (292), 178 (292), 179 (292), 182, 199
 Iwamoto, H. K., 325, 337
- J
- Jackerott, K. A., 340, 344, 357, 359
 Jackson, E. M., 251 (34), 310
 Jacobs, W. A., 23 (136), 24 (139), 61, 253 (21), 258 (20, 21, 59), 261 (59), 271 (36), 272 (36), 276, 277, 278 (14, 32, 35, 37, 57), 279 (14, 32, 35, 37, 57), 280 (32, 57, 58), 281 (14, 58), 282 (36-38, 57, 58), 283 (14, 32, 37, 58), 284 (38, 42), 286 (38, 42), 287 (41, 42), 288 (36, 38, 42), 289 (42), 290 (41), 291 (33, 39, 40), 292 (39, 40), 295 (36, 39), 296 (31, 41), 297 (30, 31), 298 (33, 39, 40), 299 (39, 40), 300 (30, 43), 301 (5, 8, 9, 10, 27, 28), 302 (27-30), 304 (30, 43), 305 (30, 43), 306 (6, 7, 11, 13, 14, 43), 307 (13, 14, 43), 308 (12, 34, 43), 310, 311, 312
 Jacobowicz, L., 158, 198
 Jaffe, H., 300 (43), 304 (43), 305 (43), 306 (43), 307 (43), 308 (43), 311
 Jang, C. S., 112 (41, 42), 118
 Janot, M. M., 50, 52, 54, 63, 234 (184), 246, 320, 335, 377 (45), 385 (72), 390 (72), 391 (97, 103), 392, 393
 Jansen, M., 325, 336
 Jantzen, E., 41 (199), 62
 Jaretsky, R., 156, 197
 Jarowski, C., 352, 361
 Jarzyński, L., 21 (118), 22 (118), 60
 Jatridès, D., 210 (103), 212 (103), 244
 Jean-Baptiste, J. A., 391 (99, 100), 393
 Jeger, O., 291 (2), 296 (62), 302, 311, 312
 Jenkins, G. L., 121 (16), 193
 Jensch, H., 325, 336
 Jensen, H. R., 210 (104), 212 (104), 229 (104), 244
 Johnson, T. B., 202 (7), 204 (7), 242, 340, 352, 353, 357

- Jones, 393
 Jones, R. Norman, 300 (47), 312
 Jordan, C. B., 341 (111), 342 (111), 344 (111), 358
 Joseph, J. P., 112 (51), 116 (51), 118
 Jowett, H. A. D., 206 (43), 207, 209 (28), 210 (28), 212 (27), 214 (28, 30, 33), 215 (28, 33), 216 (28, 29, 31, 33), 217 (29, 31, 33), 218 (32), 219 (28), 220 (34), 221, 222, 223 (33), 227 (28), 229 (28), 234 (28), 235 (28, 29, 30, 33), 236 (28-31, 33), 238 (28), 239 (28, 30), 240 (28-31), 241 (28), 242, 243
 Juneja, H. R., 108, 118
 Jungfleisch, E., 19 (107), 21 (107), 60
- K**
- Kabachnik, M. I., 142 (154), 161 (261), 196, 198
 Kadish, A. F., 112 (51), 116 (51), 118
 Kainz, G., 164 (277), 165 (277), 198
 Kalashnikov, V. P., 127 (110), 195
 Kamlet, J., 353, 361
 Kanao, S., 340 (16, 17, 50), 342, 343, 345 (71), 346, 347 (17, 71), 348, 349, 351, 352, 353, 356, 357, 358
 Kanga, D. D., 252 (8), 309
 Kao, C. H., 345 (240), 354, 360
 Kao, Y. S., 112, 114 (45), 115 (45), 117 (45), 118
 Karrer, P., 44, 62, 124 (76), 131, 132 (119), 133, 134 (123), 135 (123), 158 (119), 161 (262), 194, 195, 198, 364 (15), 365 (15), 367 (15), 368 (15), 369, 372, 378 (33), 379, 380, 381 (51), 385 (15), 386 (15, 33, 50), 389 (33), 390 (33, 50), 392
 Katsnel'son, M. M., 142 (154), 196, 226 (67), 248
 Katz, A., 267 (51), 268 (51), 310
 Kaufmann, A., 12 (91), 26, 37 (178-180), 38, 42 (210, 211), 43 (212, 213), 46 (227, 228), 60, 61, 62, 63
 Kefeli, T. Ya., 161 (261), 198
 Keil, B., 164 (276), 165, 174, 198
 Keil, F., 340, 351 (79), 352, 353, 357
 Keller, F., 270 (44a, 44b), 276 (44), 277 (44), 311, 312
 Keller, O., 364, 367 (21), 392
 Kelly, J. W., 206 (89), 244, 341, 358
 Kemperdick, 10 (82), 59
 Kenner, J., 13 (93), 29 (152), 60, 61
 Kerner, G., 3 (27), 58
 Kesztlér, F., 102, 103 (28), 104 (28), 118
 Kindler, K., 31 (155), 41, 43 (208), 44 (218), 45 (205, 219), 46 (226), 47 (219), 48 (155), 61, 62, 63, 319, 321, 324, 325, 326, 335, 336
 King, H., 24 (138), 34 (167), 37 (181), 38 (181), 44 (216), 61, 62
 Kirby, K. S., 52, 53 (253, 255), 63
 Kirkpatrick, H. F. W., 212 (153), 245, 344 (235), 360
 Kirkwood, S., 314, 315, 320, 321, 334
 Kiss, J., 346 (252), 351 (252), 361
 Klavehn, W., 353, 361
 Klein, G., 67, 98, 122 (33), 193
 Klingsberg, A., 290 (20), 293 (20), 296 (20), 311
 Klohs, M. W., 270 (44a, 44b), 276 (44), 277 (44), 306 (44a), 311, 312
 Klostermann, M., 170 (288), 198
 Kneuer, A., 167, 176, 179, 198
 Knorr, L., 38 (189), 62, 72 (25), 86 (25), 98
 Knovalova, R. A., 343, 359
 Knox, L. H., 31 (156), 34 (156), 61
 Knudsen, P., 215 (167), 246
 Knunyants, I. L., 142, 196
 Koelsch, C. F., 38, 62
 Koenigs, W., 2 (11-14, 18, 22), 3 (45, 50), 4 (12, 56, 57-59), 5 (58, 61, 65), 7 (73), 12 (89), 13 (13, 56, 58, 92), 19 (12, 14, 18, 22), 23 (64, 134), 24 (137), 25 (58, 59, 72), 26 (64, 65, 148), 28 (134, 151), 34 (11-14, 56, 134, 151), 37 (173), 38 (58, 59), 39 (191), 41 (72, 191, 201), 58, 59, 60, 61, 62
 Koepfli, J. B., 22 (130), 24 (143), 44 (216), 60, 61, 62, 112, 113 (44), 114 (44), 115 (43, 44), 117 (43, 44), 118
 Köppen, R., 272, 273 (59), 312
 Körner, W. G., 80, 81, 83 (35), 84, 85 (35), 94 (35), 96 (35), 98
 Koessler, K., 319, 335
 Kohlbach, D., 39 (194), 62
 Kohlhammer, E., 210 (36), 215 (36), 216 (36-38), 217, 218 (38), 219 (37, 38), 223 (36), 224 (36, 37), 234 (36), 235 (36), 236 (37, 38), 243

- Kolbe, A., 67 (3), 68, 98
 Kolbe, F., 34 (168), 61
 Kolesnikow, D. G., 102, 103 (30), 104 (30), 118
 Koller, G., 340, 347 (70), 351, 357
 Kolthoff, J. M., 210, 212 (98), 244
 Komzak, A., 41 (203), 62
 Konck von Norwall, F., 2 (8, 9), 58
 Kondo, H., 125 (92), 178 (293, 294), 179 (294, 296), 180 (293, 294, 297-301), 181 (293, 296, 301, 302), 182 (92, 293, 304), 194, 199
 Kondo, T., 319, 335
 Kondratyeva, A. V., 128 (111), 195
 Konek, F., 105 (34), 111 (34), 118
 Konopnicki, A., 20 (111), 60
 Konovalova, R., 121 (1), 124 (1, 81), 125 (1, 99), 126 (2, 81), 156 (81), 161 (81), 174 (1), 178 (99), 186 (99), 192, 194
 Koster, S., 270 (44a, 44b), 276 (44), 277 (44), 311, 312
 Kovács, J., 50 (239), 63
 Kovalenko, V. N., 71, 98
 Kraïzman, P. S., 210 (110), 212 (110), 244
 Kraye, O., 259 (28), 310
 Krecke, F., 107, 118
 Kreitmair, H., 123 (45), 174 (45), 193, 354, 362
 Krishna, S., 105 (5), 106 (5), 109, 111 (5, 32), 117, 118, 341, 342 (117), 343, 358
 Krishnamurti, G. V., 252 (29), 309
 Kroseberg, W., 80 (41), 81, 83, 85 (41), 86, 96 (41), 97 (41), 99
 Kubota, S., 340, 357
 Kuehl, F. A., Jr., 112, 113 (46), 114 (46), 115 (46), 117 (46), 118
 Kuffner, F., 102 (7, 16), 103 (17, 18), 104 (15, 18), 105 (15, 17), 106 (8), 107 (15), 108 (15, 31), 109, 111 (7, 15, 17, 31), 117, 118, 126 (102), 156 (102), 194
 Kuhn, R., 250 (31), 251 (31), 252, 253 (32), 258 (31), 260 (31), 266, 267 (33), 268 (33), 310
 Kuleshova, M. G., 228 (70), 243
 Kuliga, E., 23 (135), 29 (153), 30 (135, 153), 34 (135), 61
 Kunkler, M., 42 (210), 43 (212), 62
 Kunz, E., 210 (109), 227 (109), 229, (109), 230, 234 (109), 235 (109), 236 (109), 237 (109), 244
 Kunz, H., 366 (32), 392
 Kunz-Krause, H., 364 (19), 367 (19), 392
 Kupchan, S. M., 270 (45), 276, 277 (45), 306 (45), 309 (45), 312
 Kutscher, F., 202 (1, 3), 203, 204 (14), 205 (14), 242
 Kuznetsov, A. I., 127 (110), 195
- ## L
- La Barre, W., 314, 338
 Labriola, R., 69 (11), 70 (11, 17), 74, 77 (11, 30), 98
 Lachwitz, A., 80 (36), 94 (36), 95 (36), 96 (36), 98
 Ladenburg, A., 340, 349, 350, 355
 La Floresta, A., 341, 358
 La Forge, F. B., 319, 322, 336
 Lahey, F. N., 70 (19, 26), 71 (26), 73 (26), 77 (19, 26), 98
 Laidlaw, P. P., 155 (196), 197, 391, 393
 Lamberton, J. A., 70 (26), 71 (26), 73 (26), 77 (26), 78 (60), 79 (60), 98, 99
 Lambillon, J., 353, 361
 Lammers, J., 145, 146, 196
 Lampitt, L. H., 251 (34), 310
 Langenbeck, W., 216 (168), 222, 223 (169), 234 (168-170), 235 (168, 169), 239 (168, 169), 240 (168), 246
 Lavin, G. I., 296 (31), 297 (31), 301 (9), 311
 Lawson, A., 203 (14a), 204 (14b, 15a, b), 205, 242
 Lazur'evskii, G., 121 (2, 3), 124 (71), 125 (3, 100), 126 (3), 185 (3), 188, 192, 194
 Lebeau, P., 391 (103), 393
 Le Blanc, F., 341 (132), 342 (132), 358
 Lecoq, H., 344 (226), 353, 360
 Leeb, W., 90, 91 (55), 94 (55), 99
 Léger, E., 19 (107, 108), 20 (107, 108, 116), 21 (107, 123), 60, 210 (117), 230, 231 (116), 232 (116, 117), 237 (116, 117), 241 (116, 117), 244, 383 (56), 392
 Léger, M. F., 320, 321, 335
 Le Hir, A., 385 (72), 390 (72), 393

- Lehmann, G., 92, 93, 99
 Leitch, Grace, C., 124 (69), 160, 161 (69), 163 (69), 167, 170 (68), 194
 Leithe, W., 31 (158), 61, 340, 351, 357, 367, 368, 374, 378 (28), 385 (28), 389 (28), 392
 Leonard, N. J., 116 (49), 118, 123 (311, 312), 163, 164, 165, 174 (278, 312), 176 (311), 190 (324, 325), 191 (278), 192 (320), 198, 199
 Leprince, M., 317, 334
 Levi, A. A., 252 (4), 259 (4), 264 (4), 265 (4), 309
 Levin, B., 348, 361
 Levine, P., 191 (327), 199
 Lévy, M., 210 (96), 244
 Lewin, L., 332, 337
 Lewis, J. T., 331, 337
 Liang, P., 103 (12), 104 (12), 107, 111 (12), 118
 Liberalli, C. H., 123 (61), 194
 Liebl, Fr., 45 (222), 62
 Limpach, L., 68, 86 (4), 87 (4), 90, 98
 Linarix, A., 234 (183), 246
 Linstead, R. P., 191 (327), 199
 Lintner, J., 108, 111 (31), 118
 Lippmann, E., 2 (20), 19 (20), 58
 Litterscheid, F. M., 155 (194), 170, 171, 196
 Liu, J. C., 341, 342 (97), 357
 Liu, S. K., 112 (38), 118
 Livshits, R. S., 390 (103), 394
 Locker, R. H., 256 (15), 258 (15), 259 (15, 16), 260 (15), 263 (16), 265 (15, 16), 266 (15, 16), 309
 Löffler, K., 39 (193), 62
 Löw, Irmentraut, 250 (31), 251 (31), 252, 253 (32), 258 (31), 260 (31), 266, 267 (33), 268 (33), 310
 Loiseau, J., 212 (150), 245
 Losanitsch, M. S., 6 (68), 26 (68), 40 (68), 59
 Louw, P. G. J., 249 (60), 253 (60), 270 (60), 310
 Loy, S. K., 308 (23), 309 (23), 311
 Lozeron, H., 353, 361
 Lu, G., 112 (41), 118
 Ludewig, H., 55 (257), 63
 Ludueña, F. P., 323, 330, 331, 333, 334, 336, 337, 338
 Ludwiczakówna, Rufina, 18 (99), 20 (111), 21 (118), 22 (118, 127) 33 (99), 47 (229), 60, 63
 Luff, A. P., 272, 273 (68), 274 (68), 277, 297 (68), 298 (69), 312
 Luis, Ethel M., 348 (148), 358
 Lukes, R., 143, 196
 Lumholtz, C., 332, 337
 Lutz, R. E., 44 (216), 62
 Lynch, G. R., 212 (145), 245
- ### M
- Ma, Roberta M., 250 (35), 253 (27, 35), 267 (26), 268 (26), 310
 Ma, Tsu-Sheng, 210 (128), 234 (128), 245
 Maag, R., 6 (69), 26 (69), 40 (69), 59
 Maass, E., 144 (166), 196
 McAllister, D. P., 314 (174), 338
 Macbeth, A. K., 273 (46), 300 (46), 304 (46), 312
 McCausland, H., 341 (122, 125), 358
 MacDonald, C. A., 344 (206), 360
 MacDonald, S. F., 57 (262), 63
 McEvoy, F. J., 112 (51), 116 (51), 118
 McEwen, W. E., 390 (101), 394
 McGillivray, W. A., 256 (15), 258 (15), 259 (15), 260 (15), 265 (15), 266 (15), 309
 Macheboeuf, M., 344 (229, 230), 360
 Mack, H., 345 (239), 360
 McKenzie, A., 348 (148), 358
 McKenzie, A. W., 69 (61), 99
 McMillan, A., 9 (79), 59
 Madsen, H., 383 (57), 393
 Magalhaes, A., 144 (164, 169), 146, 196
 Magendie, 364, 366 (10), 391
 Major, Y., 126 (106), 195
 Malesh, W., 270 (44a, 44b), 276 (44), 277 (44), 311, 312
 Mallmann, F., 10 (85), 59
 Malosse, T., 125 (93, 94), 126 (93, 94), 175, 194
 Mangan, J. L., 124 (85), 125 (85), 194
 Mannich, C., 353, 361
 Manske, R. H. F., 121 (22), 122 (22), 124 (86, 87), 125 (22), 127 (22), 128, 170 (22), 186 (22), 188 (22, 87), 193, 194, 199, 247, 340, 352, 353, 357, 363
 Mararo, I. L., 128 (111), 195
 Marinesco, G., 333, 338
 Marion, L., 121 (7, 8, 18, 19, 22), 122 (7, 8, 22, 32), 123 (18, 19, 68, 309, 310,

- 311, 312), 124 (7, 8, 32, 86), 125 (19, 22, 309), 126 (7, 8, 19, 32, 310), 127 (7, 8, 18, 22, 32, 310, 315), 128, 130 (8), 144 (7, 32), 156 (19, 32), 163 (310), 166 (7, 8, 19, 32, 68), 167 (19), 170 (18, 19, 22), 174 (19, 310, 312, 315), 175 (309, 310), 176 (309, 310, 311), 185 (18), 186 (22, 315, 323), 187 (8, 310, 323), 188 (8, 7, 22, 32), 191, 192 (320), 192-194, 199, 300 (47), 312, 314, 315, 320, 321, 334
- Markham, C., 1 (1), 58
- Marmé, W., 143, 196
- Marschall, O., 23 (135), 30 (135), 34 (135), 61
- Maruyama, M., 177 (292), 178 (292), 179 (292), 199
- Marx, W., 157, 161, 190, 197, 198
- Mascherpa, P., 353, 361
- Masché, M., 212 (150), 245
- Mashkovskii, M. D., 122 (42), 193
- Massagetov, P. S., 341, 358
- Massatsch, C., 210 (127), 234 (127), 245
- Masucci, P., 341 (109), 358
- Matsuska, F., 390 (79), 393
- Matthes, H., 210 (129), 212 (129), 217 (129), 234 (129), 245
- Maurel, E., 390 (78), 393
- Maximova, T., 121 (26, 27), 161 (26), 183 (26), 184 (26), 185 (27), 193
- Mayer, F., 22 (129), 60, 123 (60), 194
- Mayer, M., 234 (180), 246
- Mayer, Margarete, 121 (24), 124 (24), 183 (24), 184 (24), 193
- Mead, J. F., 22 (130), 24 (143), 60, 61, 112, 113 (44), 114 (44), 115 (43, 44), 117 (43, 44), 118
- Medler, Jeanne D., 344 (176), 359
- Meiner, H., 340 (79), 351 (79), 352 (79), 353, 357
- Meisenheimer, J., 39 (192), 62
- Melville, 383 (54), 392
- Mengel, A., 3 (45), 37 (173), 59, 61
- Men'shikov, G. P., 121 (25), 183 (306), 184 (25), 185 (25), 193, 199, 317, 318, 334
- Merek, E., 215 (166), 228, 229 (165), 230, 236 (165), 241 (165), 246, 339, 340 (5), 355
- Merek, G., 272, 273 (48), 312
- Merkulov, L. G., 142 (156), 196
- Metcalfe, T. P., 40, 62, 140 (137), 195
- Meyer, C., 124 (75), 126 (75), 194
- Meyer, H., 42 (209), 62, 67 (5), 69, 98, 207, 213, 214 (23, 162), 220 (23), 230 (163, 164), 236 (164), 242, 246
- Mikhlina, E. E., 232, 246
- Miller, E. R., 340, 346, 350, 356
- Miller, W. von, 6 (66), 7 (71), 9 (71), 25 (71), 59
- Mills, E. J., 156, 197
- Mills, J., 37 (176), 61
- Minasyan, S. M., 250 (36), 310
- Misner, R. R., 38 (184), 62
- Mitchell, Agnes G., 348 (148), 358
- Mitchell, W., 346, 347 (241), 360
- Mitra, S. K., 155 (189), 196
- Miura, K., 339, 355
- Moffat, J., 115, 118
- Mohr, H., 297 (22), 304 (22), 311
- Molnar, G. D., 204 (14b), 242
- Momotani, K., 353, 361
- Monnet, R., 345 (238), 360
- Montavon, M., 296 (62), 312
- Mookerjee, A., 69 (15), 71 (15), 76 (15), 98
- Mooney, J., 332, 337
- Moore, E. E., 345 (236, 276), 360, 361
- Moore, M., 290 (20), 292 (64), 293 (20), 296 (20), 299 (64), 311, 312
- Moore, Marjorie B., 345 (276), 361
- Moran, W. J., 38 (190), 62
- Moraw, H. O., 344 (202), 360
- Morgan, F. P., 332, 337
- Morgan, W. McG., 140 (136), 141, 142 (146), 160, 161 (260), 163, 168, 173, 195, 198, 251 (19), 253 (19), 260 (19), 310
- Morin, R. D., 327, 338
- Morley, H. V., 204 (14b), 242
- Morozovitch, P., 270 (49a), 306 (49a), 312
- Morris, R. C., 109 (21), 111 (21), 118
- Morrison, D., 38 (190), 62
- Morrison, Helen S., 330 (128), 337, 353, 361
- Moschkin, P. A., 41 (200), 62
- Mosettig, E., 264 (52), 267 (51, 52), 268 (51), 310
- Mosher, H. S., 296 (49), 312
- Moss, A. R., 315, 334
- Moureu, C., 156 (203, 204, 206), 157 (217,

- 218, 219, 222-248), 158 (251), 163, 197, 198
 Moyse-Mignon, H., 69 (13), 98
 Müller, H., 10 (83), 59
 Müller, H. K., 264 (52), 267 (52), 310
 Müller, J., 325, 333, 336
 Müller, O., 80, 81, 82, 84 (39), 86 (39), 92, 94 (39), 97 (39), 99
 Müller, W., 84 (43), 85 (43), 94 (43), 95 (43), 96 (43), 99
 Mukherjee, B., 383 (53), 392
 Mulas, Maria, 341, 342 (142), 358
 Muller, F., 210 (97), 212 (97), 244
 Munch, J. C., 344 (181), 359
 Munier, R., 344 (229, 230), 360
 Murakami, K., 180 (302), 199
 Muruzabal, A., 74, 77 (30), 98
 Myers, G. S., 270 (49a), 306 (49a), 312

N

- Nagai, N., 339, 340, 342, 347 (17), 348, 349, 351, 352, 355, 356, 358
 Nagel, A., 354, 362
 Nakamura, S., 180 (298), 199
 Nakanishi, S., 74, 76 (28), 78 (28), 98
 Narang, K. S., 103 (24), 104 (5, 24), 105 (5, 24), 106 (5), 107, 108 (33), 109, 111 (5, 32, 33), 117, 118
 Narkuziev, T., 121 (14), 122 (14), 124 (14), 193
 Natradze, A. G., 232, 246
 Naumann, W., 23 (135), 29 (153), 30 (135, 153), 34 (135), 61, 230 (176), 246
 Needham, G. H., 341 (110), 358
 Neff, H., 351, 361
 Nehring, P., 80, 81, 83 (36), 84, 94 (36), 95 (36), 96 (36), 98
 Neill, K. G., 78 (58), 99
 Neresheimer, J., 39 (192), 62
 Neuberg, C., 353, 361
 Neumann, G., 20 (115), 60
 Newberne, R., 332, 337
 Newbold, R. P., 252 (17), 259 (17), 263 (17), 264 (17), 265 (17), 266 (17), 310
 Newton, Eleanor B., 202 (7), 204 (7), 242
 Nicolitch, V., 340 (52), 356
 Nielsen, C., 341 (122, 125), 358
 Nikawitz, E., 102 (6), 103 (6), 104 (6), 105 (6), 106, 111 (6), 117
 Nikitin, I. M., 142 (157), 196
 Nikolai, F., 31 (160), 61, 340 (61), 351 (61), 357
 Nishimura, K., 179, 182 (304), 199
 Nietzsche, F., 163, 174 (271), 198
 Noda, K., 182 (303), 199
 Norkina, Sophie S., 121 (4, 9, 10, 14, 21, 26, 27), 122 (4, 14), 123 (9, 10, 53), 124 (14), 125 (4), 126 (4, 9, 10, 21, 53), 127 (4, 21), 161 (26), 166 (9), 169 (4), 183 (26), 184 (26), 185 (27), 186 (4, 21), 187 (4, 21), 192, 193
 Nottbohm, F. E., 123 (60), 194
 Numano, S., 221, 236 (171), 246
 Numerof, P., 276 (21), 306 (27a), 311

O

- Obata, T., 69 (14), 98
 Oberlin, M. L., 80, 98
 O'Byrne, Sister Michael Edward, 209 (95), 244
 Ochiai, E., 124 (92), 177 (292), 178, 179 (292), 180 (298, 300, 301), 181 (293, 301, 302), 182 (92, 293, 303, 304), 194, 199
 Oddo, G., 249 (38), 251 (38), 252 (37, 38), 264 (38), 310
 Oechler, F., 110, 111 (26), 118
 Oechsner de Coninck, W., 3 (47, 48), 38 (47), 59
 Ölschlägel, C., 340, 349, 350, 355
 Ogata, A., 71, 98, 340, 350, 356
 Ohegyi, G., 346 (252), 351 (252), 361
 Ohta, T., 69, 72, 74, 76 (8), 98
 Okolskaya, T., 187, 199
 Oliverio, A., 344 (193), 359
 Olivier, M., 322, 336
 Oliviero, A., 210 (126), 234 (126), 245
 Oparina, M. P., 41 (202), 62
 Openshaw, H. T., 367 (38), 373, 375, 376 (38, 41, 47), 377, 380 (38), 381, 386 (38, 47), 390 (38, 47, 102), 392, 394
 Orekhov, A. P., 121 (1, 2, 4, 9, 10, 14, 21, 25-28), 122 (4, 14), 123 (9, 10, 53), 124 (1, 14, 80, 81, 82), 125 (1, 4, 80, 99, 101), 126 (2, 4, 9, 10, 21, 53, 81, 101), 127 (4, 21), 156 (81), 161 (26, 81, 261), 166 (9), 169, 174 (1), 178

- (82, 99), 183 (26, 306), 184 (25, 26, 28), 185 (25, 27, 28), 186 (4, 21, 99, 101), 187 (4, 21), 188, 192, 193, 194, 198, 199, 343, 359
 Ossatinsky-Portnoy, E., 344 (192), 359
 Ostemberg, Z., 318, 334
 Ottmann, W., 41 (204), 62
 Ouellet, J., 122 (32), 123 (68, 310), 124 (32), 126 (32, 310), 127 (32, 310), 144 (32), 156 (32), 163 (310), 166 (32, 68), 169, 174 (310), 175 (310), 176 (310), 186, 187 (310), 190 (32), 193, 194, 199
 Overhoff, J., 205 (17), 242
- P**
- Paal, C., 107 (13, 14), 118
 Pailer, M., 367 (34), 373, 374, 375 (37), 376 (40), 377, 379 (34), 385 (36, 49), 386 (40), 389 (34, 36, 40, 49), 392
 Pak, C., 354, 355, 362
 Palkin, S., 384, 393
 Pallares, E. S., 102, 118
 Panashchenko, A. D., 142 (158), 196
 Papaioanou, G., 80, 82 (47), 84 (47), 88 (47), 97 (47), 99
 Paris, G. A., 344 (184), 359
 Paris, R., 69 (13), 98
 Parodi, D., 207, 242
 Partheil, A., 144 (167, 168, 170), 145, 146, 149, 170, 196, 198
 Pasternack, R., 42, 43 (208, 214), 44, 62
 Pasteur, L., 6, 9 (70), 24, 59, 61
 Patel, R. P., 155, 156 (199), 197
 Patrick, J. B., 54 (256), 63
 Paul, A. E., 344 (203), 360
 Paul, B. H., 50 (240), 63, 206 (80), 244, 364, 392
 Paul, W., 212 (155), 245
 Pauly, H., 203 (13), 223, 229 (172), 230 (176), 237 (172), 242, 246
 Pawlicki, P., 157 (249), 198
 Pedinelli, M., 320, 336
 Pelletier, J., 2, 58, 364 (10), 366, 391, 392
 Pelletier, S. W., 312
 Penau, H., 391 (97), 393
 Perkin, W. H., Jr., 35 (170), 61, 232 (177), 246
 Péronnet, M., 341, 358
 Perrot, E., 364 (2), 383 (2), 391
 Perry, F., 50 (247), 63
 Peschke, W., 319, 324, 325, 326, 335, 336
 Pesez, M., 344 (170, 171), 359
 Petit, A., 207, 208 (50), 209 (50), 210 (50, 51), 214, 215 (50), 229, 234 (50, 51, 179), 235 (50), 237 (49), 238 (50), 239 (50, 179), 240 (50), 243, 246
 Petruccio, V., 332, 337
 Peyer, H., 38, 42 (210), 43 (212), 62
 Peyer, W., 344 (217), 360
 Pfannl, M., 20 (110), 60
 Pfitzinger, W., 3 (44), 37 (171, 172), 59, 61
 Phillips, A. P., 346, 361
 Piantanida, M., 39 (194), 62
 Pictet, A., 38, 42 (184), 62
 Pikl, J., 80, 81 (48), 82 (49), 84 (49), 89 (48), 92, 93, 94 (48, 49), 97 (48, 49), 99
 Pillai, K. V., 355, 362
 Pines, S. H., 140 (316), 199
 Pinner, A., 209 (39), 210 (36, 39), 214 (39), 215 (36, 39), 216 (36-39), 217 (39), 218 (38), 219 (37, 39, 41), 220, 221 (44), 222, 223 (36, 39, 40, 41), 224 (36, 37, 38, 40), 234 (36, 39), 235 (36, 39, 41), 236 (38-41), 239 (39), 243
 Pischimuka, P., 321, 336
 Pittenger, P. S., 344 (224), 360
 Platzer, N., 102 (16), 103 (17, 18), 104 (15, 18), 105 (15, 17), 107 (15), 108 (15, 29), 109 (19), 111 (15, 17, 19, 27, 29), 118
 Plugge, P. C., 122 (34, 35), 124 (79), 178 (79), 190 (35), 193, 194
 Podwyssotzki, 366, 392
 Pöhl, J., 208 (91), 210 (91), 212 (92), 244
 Pöhm, M., 123 (313), 176, 177, 190, 191 (313), 199
 Poethke, W., 272 (52), 274, 275 (50, 51), 276 (51), 279 (52), 298 (52), 306, 307 (51), 308 (51), 312
 Pohorsky, J., 344 (232), 360
 Poljakova, A. M., 225 (60, 61, 63), 226 (66, 67), 227 (60, 61, 63-65), 232, 235 (63), 243
 Polonovski, Max, 24 (142), 61, 207, 208 (50), 209 (50, 56), 210 (50, 51), 214 (56), 215 (50), 216 (53, 54), 222, 224, 229, 234 (50, 51, 56), 235 (50, 52, 53)

- 236 (52, 53, 54), 237 (49), 238 (50),
239 (50, 52, 53, 56), 240 (50, 52-54,
56), 240 (52), *243*
- Polonovski, Michel, 24 (142), *61*, 207,
208 (50), 209 (50, 56), 210 (50, 51),
214 (56), 215 (50), 216 (53, 54), 222,
224, 229, 234 (50, 51, 56), 235 (50,
52, 53), 236 (52, 53, 54), 237 (49), 238
(50), 239 (50, 52, 53, 56), 240 (50,
52-54, 56), 241 (52), *243*
- Poole, Janet B., 253 (27), *310*
- Porschinski, K., 376 (40), 377, 379, 385
(49), 386 (40), 389 (40, 49), *392*
- Portnoy, E. Ossatinsky, 344 (192), *359*
- Potter, C. E., 220 (34), *243*
- Power, F. B., 124 (88), 144, *194*
- Prantl, 340
- Prelog, V., 12 (90), 26 (149), 28 (150), 31
(157), 32, 39 (195, 196), 41 (203), 45
(220), 47 (232), 50 (90), 51 (250), 52,
54, *60*, *61*, *62*, *63*, 140 (138, 139), *195*,
251 (39), 253 (39), 255 (40), 256 (40),
258 (39, 40), 260 (40), 261 (40), 261
(40), 302, *310*, *392*
- Prentiss, D. W., 332, *337*
- Preobrashenski, N. A., 217 (57), 225
(60-63), 226 (58, 59, 66, 67), 227 (57,
58-65), 228 (70, 71), 232, 234 (59),
235 (63), 236 (59), *243*, 390 (103), *394*
- Preobrashenski, W. A., 225 (60-63), 226
(58, 59, 66, 67), 227 (58-65), 228
(71), 232, 234 (59), 235 (63), 236
(59), *243*
- Price, C. C., 116 (49), *118*
- Price, J. R., 69 (61), 70 (19, 26), 71 (26),
76 (19, 26), 78 (60, 61, 63), 79 (60),
98, *99*
- Primo, E., 125 (95), 126 (95), 175, *194*
- Proskurnina, N., 121 (1, 2), 124 (1, 80,
82), 125 (1, 80), 126 (2), 174 (1), 178
(82), 188, *192*, *194*, *199*
- Proštenik, M., 12 (90), 45, 50 (90), *60*
- Pschorr, R., 74, *98*
- Purvis, J. E., 209 (94), *244*
- Puyal, J., 340 (49), 351, *356*
- Pyman, F. L., 206 (43), 210 (48), 220 (44,
47), 221, 222 (44), 224 (47), 228 (45),
230 (46), 231 (46), 232, 234 (48), 237
(46, 48), 241 (46, 48), *243*, 364, 365
(16, 23, 24), 366, 368 (23), 369 (13),
370 (24), 372 (24), 378 (16), 379, 382,
383 (16), 384 (16, 67), 385 (13, 16),
386 (13, 16, 23), 387 (13, 16, 23, 24),
388 (13, 16, 24), *392*
- Q
- Quazilbash, N. A., 341, *358*
- Quevauviller, A., 391 (100), *393*
- Quinquaud, A., 390 (76), *393*
- R
- Rabe, P., 7 (74, 75), 9 (79), 10 (80, 87), 16
(95, 97, 100, 101), 19 (106), 23 (97,
135), 25 (95, 146), 29 (75, 153), 30
(76, 97, 153), 31 (154, 155), 32 (94,
162), 33 (97, 100), 34 (97, 100, 135,
168, 169), 38, 41 (199, 205), 42 (206),
43, 44, 45 (76, 205, 219, 224), 46
(225, 226), 47 (146, 188, 219, 230,
231), 48 (154, 155), 50 (101), *59-63*,
340, 350, *356*
- Rabinovich, M., 124 (81), 125 (99), 126
(81), 156 (81), 161 (81), 178 (99), 186
(99), *194*
- Ramage, G. R., 138 (131), 139 (130, 133),
140 (130), 154 (133), 168 (131), *195*
- Ramirez, F. A., 328, *338*
- Rammstedt, O., 210 (129), 212 (129), 217
(129), 234 (129), *245*
- Ramsay, D. A., 300 (47), *312*
- Rao, P. L. Narasimha, 155 (191, 192), *196*
- Raoul, Y., 320, 321, *335*
- Raper, R., 121 (23), 122 (23), 127 (23),
135, 138 (131), 139 (133), 140 (136,
137), 141, 142 (146), 154 (133), 158,
159 (126), 160 (258), 161 (260), 163
(259), 164, 167 (259), 168 (131, 258,
259), 169, 171 (259), 173, 188 (23),
193, *195*, *198*, 251 (19), 253 (19), 260
(19), *310*, 315, 316, 323 (9, 10, 11),
334
- Rapport, M. M., 22 (130), *60*
- Raub, A., 323, *336*
- Rauch, C., 162 (267), 163, 165, 174 (267),
187, *198*
- Rauwerda, A., 122 (35), 190 (35), *193*
- Rây, J. N., 103 (4, 24), 104 (4, 5, 24), 105
(5, 24), 106 (5), 107, 108 (33), 109,
111 (5, 32, 33), *117*, *118*

- Raymond-Hamet, M., 50 (249), 63, 80, 99, 330, 331, 333, 337, 338, 344 (169), 354, 359, 362
- Read, B. E., 340, 341 (125), 342 (97, 101, 105), 343, 344 (104, 187), 345 (107), 354, 355, 357, 358, 359, 362
- Redmann, C. E., 70 (54), 83 (54), 99
- Regnier, J., 391 (100), 393
- Reich, H., 309
- Reichard, C., 211 (139), 245
- Reichstein, T., 309, 366, 370, 373 (22), 374, 379, 385 (22), 387 (22), 389 (22), 392
- Reilhes, R., 320, 335
- Reimers, F., 212 (143), 245, 344 (227, 228), 360
- Reinwein, H., 202 (2), 242
- Reitmann, J., 162, 163, 198
- Remfry, P., 42, 62
- Renfrew, A. G., 23 (133), 60
- Renshaw, R. R., 37 (174), 61
- Reti, L., 320, 321, 322, 323, 324, 328, 329, 331, 335, 336
- Reuter, C., 202 (4), 203 (12), 204 (4, 12), 205 (4), 242
- Reyman, J., 21 (122), 60
- Reynolds, T. M., 106, 117
- Reynolds, W. C., 206 (84), 244
- Režek, A., 39 (194), 62
- Reznek, S., 344 (208), 360
- Rhino, F., 340 (58), 356
- Ribas, I., 125 (95, 95a), 126 (95, 95a), 175 (328, 329, 330), 194, 199
- Richter, D., 333, 338, 354, 362
- Ricketts, J., 122 (40), 124 (40), 125 (40), 127 (40), 178 (40), 190 (40), 193
- Riedl, K., 177, 199
- Rietschel, H. G., 330, 337
- Rigby, W., 312
- Rimington, C., 203 (14a), 204 (15a), 205, 242
- Ritchie, E., 78 (59, 63), 99, 141, 166, 199
- Roberts Alcorta, M. E., 253 (41), 310
- Robinson, R., 57 (261), 63, 106, 117, 273 (46), 300 (46), 304 (46), 312, 369, 376, 392
- Roca, J., 316, 334
- Rochelmeyer, H., 252 (42, 43, 46), 255 (23, 24, 44, 45), 256 (45), 257 (23, 48), 258 (42, 46), 259 (46, 49), 260 (23, 42, 45), 261 (44, 45), 262 (45, 48), 263 (42, 43, 46), 264 (46), 265 (42, 43, 46, 49), 266 (49), 310
- Rönsberg, H. E., 162 (268), 174 (268), 198
- Rogers, E. F., 343, 359
- Rogers, L., 363, 390, 393
- Rohde, G., 6 (66), 7 (71), 9 (71), 25 (71), 59
- Rooke, H. S., 251 (34), 310
- Roques, F., 210 (117), 230, 231 (116), 232 (116, 117), 237 (116, 117), 241 (116, 117), 244
- Roques, H., 344 (183), 359
- Rose, C. L., 114 (47), 118
- Rosenfeld, A. D., 102, 103 (30), 104 (30), 118
- Rosenmund, K. W., 319, 321, 325, 335, 336
- Rosenthaler, L., 210 (118-124), 229 (119), 234 (120, 121, 124), 244, 245, 324, 336, 344 (196), 359
- Rosenthaler, R., 344 (185), 359
- Rosin, J., 345 (239), 360
- Rossi, L., 344 (220), 360
- Rossi, O. A., 344 (220), 360
- Rothchild, S., 140 (141, 143), 143, 195
- Rothen, A., 256 (50), 269 (50), 310
- Rothlin, E., 12 (91), 26, 60
- Rouhier, A., 332, 337
- Roylance, J., 210 (48), 221, 230, 234 (48), 237 (48), 243
- Rubinstein, M. M., 317, 334
- Rüttner, O., 372, 378 (33), 379, 380, 381, 386 (33, 50), 388 (33), 390 (33, 50), 392
- Rumpf, F., 325, 336
- Runne, E., 340 (37), 356
- Runne, H., 80 (40), 82, 83 (40), 84 (40), 90 (40), 92 (40), 94 (40), 95 (40), 97 (40), 99
- Russell, W. E., 121 (20), 122 (20), 124 (84), 125 (20, 84), 144 (20), 170 (20), 178 (84), 190 (20, 84), 193, 194
- Russell, W. F., 23 (135), 30 (135), 34 (135), 61
- Ruzicka, L., 41, 45 (221, 222), 62, 296 (62), 312
- Rydon, H. N., 173 (290), 198
- Rymill, F. E., 344 (206), 360

S

- Sadykov, A., 121 (3, 29), 124 (70, 71), 125 (3, 100), 126 (3), 142 (155), 183 (29), 185 (3), 192, 193, 194, 196
- Sah, P. P. T., 210 (128), 234 (128), 245, 340, 352, 357
- Saito, K., 282 (56), 284 (56), 288 (56), 290 (54), 298 (54, 55), 312
- Saiyed, I. Z., 252 (8), 309
- Salis, Edina, 341, 342 (142), 358
- Salway, A. H., 124 (88), 144, 194
- Salzberger, G., 272 (53), 274, 275, 276 (53), 312
- Samdahl, B., 210 (100), 244
- Sánchez, A., 125 (95), 126 (95), 175, 194
- Sánchez, J. A., 212 (147), 245, 344, 360
- Sánchez, J. S. B., 353, 361
- Sato, Y., 264 (52), 267 (51, 52), 268 (51), 277, 278 (57), 279 (57), 280 (57, 58), 281 (58), 282 (58), 283 (58), 284 (42), 286 (42), 287 (41, 42), 288 (42), 289 (42), 290 (41), 291 (40), 292 (40), 296 (41), 298 (40), 299 (40), 310, 311, 312
- Schaffnit, K., 261 (25), 262 (25), 310
- Schaumann, O., 134, 135 (124, 125), 142 (124, 125), 195, 196, 354, 362
- Schirm, M., 158, 162 (265), 198
- Schläger, J., 90, 91 (55), 94 (55), 99
- Schlagdenhauffen, F. R., 80, 98
- Schlittler, E., 262 (53), 268 (53), 310
- Schlossberger, 391 (94), 393
- Schlossmann, H., 354, 362
- Schmalfuss, H., 318, 322, 335
- Schmid, H., 165 (318), 199, 381, 392
- Schmidt, C. F., 340, 354, 357
- Schmidt, E., 123 (51, 54), 124 (54, 73, 77), 126 (54, 77), 131, 134 (121), 135 (121), 136 (121, 127), 137 (127, 128), 141 (127), 143 (127), 156 (77), 157 (128), 167, 170, 193, 194, 195, 198, 272, 273 (59), 312, 340, 345 (20, 21, 25, 28, 29, 30, 39), 350, 351, 353, 354, 356, 357
- Schmidt, L. H., 114 (47), 118
- Schmidt, M. von, 3 (55), 59
- Schneider, W., 7 (75), 39 (192), 59, 62
- Schniderschitsch, H., 26 (147), 61
- Schoeffel, E., 31 (159), 61, 340 (59), 351 (59), 352, 356
- Schoen, K., 344 (211), 360
- Schoenheimer, R., 315, 334
- Schöpf, C., 92, 93, 99, 110, 111 (26), 118, 134, 135, 136 (121, 127), 137 (127, 128), 141, 143 (127), 157 (128), 158 (251), 161, 195, 198, 255 (54), 257 (54), 260 (54), 261 (54), 262 (54), 310, 323, 336
- Schoetzow, R. E., 341 (110), 358
- Scholtz, M., 157 (249, 250), 198
- Scholz, C. R., 330 (128), 337, 353, 361
- Schtschukina, M. N., 226 (59), 227 (59), 234 (59), 236 (59), 243
- Schubert, A., 2 (21), 19 (21), 58
- Schürhoff, P. N., 341, 344 (99), 357
- Schulek, E., 50 (239), 63
- Schuler, W., 10 (80), 47 (231), 59, 63
- Schultz, F. H., 355 (300), 362
- Schultze, A., 38 (188), 47 (188), 62
- Schusta, F., 67, 98
- Schwarz, A., 273 (16, 18), 311
- Schwarz, H. P., 297 (16), 302 (18), 304 (16), 305 (18), 311
- Schwarz, R., 209 (39), 210 (39), 214 (39), 215, 216 (39), 217 (39), 219 (39), 220, 221, 223 (39, 40), 234 (39), 236 (39, 40), 239 (39), 243
- Schwyzer, J., 273 (60), 312
- Scott, C. C., 155 (197), 197
- Searle, C. E., 204 (15b), 242
- Seebeck, E., 270 (60b), 273 (60a), 274 (60a), 277, 297, 300 (60a), 304 (60a), 312
- Seekles, L., 19 (103), 60
- Seelye, R. N., 256 (15), 258 (15), 259 (15), 260 (15), 265 (15), 266 (15), 309
- Seidel, C. F., 45 (222), 62
- Seiwerth, R., 45 (220), 47 (232), 62, 63, 140 (138), 195
- Sen, J. N., 102, 103, 104 (2), 105 (2), 111 (2), 117
- Seone, M. Concepción, 175 (328), 199
- Ser, Susanne, 353, 361
- Seshadri, T. R., 252 (29), 309
- Sharp, T. M., 391 (93), 393
- Shaw, G. E., 52, 53 (253), 63
- Shibata, B., 158 (254), 198
- Shinozaki, Y., 319, 335
- Short, W. S., 164, 198
- Shrapnel, B. C., 391 (98), 393
- Shupe, I. S., 212 (144), 245
- Sicé, J., 344 (173), 359

- Siebert, C., 167, 169 (282), 198
 Sieckmann, W., 123 (45), 174 (45), 193
 Sievers, A. F., 341 (131), 358
 Siguier, F., 391 (96), 393
 Simon, I., 341, 344 (144), 358
 Sivadjian, J., 344, 359
 Skita, A., 23 (131), 60, 340, 351, 352, 353, 357
 Skraup, Zd. H., 2 (19, 21), 3 (16, 25, 28, 30, 31, 40, 51, 52, 53), 5 (60, 62, 63), 6 (67), 19 (16, 19, 21, 105), 21 (120), 26 (60), 58, 59, 60
 Slotkin, J. S., 313 (174), 338
 Slotta, K. H., 319, 325, 326, 333, 335, 336
 Smith, S., 342, 348, 349, 358
 Sobel, P., 321, 336
 Sohn, E., 234 (181), 246
 Soine, T. O., 121 (16), 193
 Soldaini, A., 123 (57), 167, 193, 198
 Solomon, W., 20 (112), 21 (112, 125), 22 (128), 28 (112), 60
 Soltys, A., 251 (56), 255 (55), 258 (56), 260 (55, 56), 261 (55), 262 (55), 310
 Sommer, H., 323, 336
 Sorm, F., 143, 164 (276), 165, 174, 196, 198
 Šoštarić, N., 39 (195), 62
 Spänhauer, F., 340 (43), 345 (43), 347 (43), 351 (43), 356
 Späth, E., 67 (3), 68, 80, 81 (48), 82 (47, 49), 84, 86, 87, 88 (45-47), 89 (48, 56), 92, 93, 94 (45, 48, 49), 95 (45), 96 (46), 97 (46-49), 98, 99, 102, 103 (6, 17, 18, 28), 104 (6, 7, 15, 18, 28, 35), 105 (6, 15, 17), 106 (8), 107 (15), 108 (15, 29, 31), 109 (19), 111 (6, 7, 15, 17, 19, 27, 29, 31), 117, 118, 121 (24), 124 (24), 126 (102), 148, 149, 150 (181), 151 (181), 153 (186), 154, 155, 156 (102), 159, 171, 173, 183 (24), 184 (24), 193, 194, 196, 198, 210 (109), 227 (109), 229 (109), 230, 234 (109), 235 (109), 236 (109), 237 (109), 244, 313, 320, 321, 325, 327, 328, 334, 336, 337, 338, 340, 347 (68, 69, 70), 351, 352, 357, 361, 367 (34), 368, 373, 374, 378 (28), 379 (34), 385 (28), 389 (28, 34), 392
 Spasokukotskii, N., 124 (70), 194
 Spasski, L., 170, 198
 Spehr, P., 342, 358
 Spencer, C. F., 112, 113 (46), 114 (46), 115 (46), 117 (46), 118
 Speyer, E., 24 (140), 61
 Spruth, H. C., 341 (122), 358
 Stace, N. E., 252 (17), 259 (17), 263 (17), 264 (17), 265 (17), 266 (17), 310
 Statham, F. S., 13 (93), 60
 Staub, H., 364 (18), 368, 369, 370, 371, 386 (30), 392
 Steiger, K., 383 (61), 393
 Stempel, B., 344 (213), 360
 Stenhouse, J., 156, 197
 Stern, Erika, 140, 151 (188), 157, 161 (188), 171, 173, 183, 184 (188), 195, 196
 Stern, P., 47 (232), 63
 Stevens, P. G., 352, 361
 Stewart, O. C., 313 (174), 338
 Stietzel, F., 39 (193), 62
 St. John, J. H., 391 (84), 393
 Stockberger, W. W., 206 (89), 244
 Stockmann, R., 343, 359
 Stoll, A., 208 (90), 244, 270 (60b), 273 (60a), 274 (60a), 277, 297, 300 (60a), 304 (60a), 312
 Stollberg, K., 107 (13), 118
 Stolz, Hilde, 210 (108), 229 (108), 234 (108), 236 (108), 244
 Strecker, A., 2 (6), 58
 Stuart, E. H., 342, 349, 358
 Stuckert, G. V., 69, 71 (16), 98
 Stützel, H., 259 (49), 265 (49), 266 (49), 310
 Sugimoto, H., 290 (54), 298 (54, 55), 312
 Suida, W., 210 (105), 244
 Sumuleanu, C., 74, 98
 Suszko, J., 18 (98, 99), 20 (109, 111, 113), 21 (109, 118, 121, 122), 22 (118, 127), 24 (141), 33 (98, 99, 164), 34 (165), 60, 61
 Suto, K., 341 (109), 358
 Swan, G. A., 142 (153), 196
 Syrneva, Yu. I., 317, 330, 334
 Szelag, F., 33 (164), 61
 Szpilfogel, S., 251 (39), 253 (39), 255 (40), 256 (40, 57), 258 (39, 40), 260 (40), 261 (40), 262 (40, 57), 310
 Szyska, G., 325, 326, 336

T

- Tabern, D. L., 345 (236, 275), 360, 361
 Tainter, M. L., 204 (15), 242, 330 (128), 337, 353, 354, 361, 362
 Takahashi, D., 339, 355
 Takaoka, M., 290 (54), 298 (54, 55), 312
 Tamm, C., 282, 284 (61), 286 (61), 287 (61), 288 (61), 289 (61), 312
 Tan, S., 112 (38), 118
 Tancred, Edwin, 210 (100), 244
 Tanret, C., 202 (5), 204 (5, 5c), 205 (5), 242
 Taran, E. N., 206 (83), 244
 Tarlé, M., 341 (112), 342 (112), 358
 Tax, S., 313 (174), 338
 Taylor, W. I., 50, 52, 54, 63, 392
 Taylor, W. S., 124 (83), 125 (83), 144 (83), 178 (83), 190 (83), 194
 Tenniswood, C. R. S., 159, 163 (259), 167 (259), 168 (259), 171 (259), 198
 Teresaka, M., 78 (62), 99
 Terry, R. E., 341 (123), 358
 Teske-Guttmann, R., 10 (87), 59
 Thielepape, E., 37, 38 (186), 62
 Thierfelder, K., 93, 99
 Thomä, O., 134, 135, 136 (121), 195
 Thomas, W. C., 70 (19), 77 (19), 98
 Thomis, G. N., 210 (103), 212 (103), 244
 Thoms, H., 69, 71 (6), 72, 76 (6, 7), 98, 167, 198
 Thron, H., 50 (234, 238), 63
 Tipson, R. S., 38 (190), 62
 Tjaschelowa, L. S., 41 (200), 62
 Tomanek, A., 18 (98), 33 (98), 60
 Tonkin, Isabel M., 112 (39), 118
 Torquati, T., 320, 335
 Torres, C., 340 (51), 356
 Trautz, M., 209 (93), 244
 Treupel, W., 10 (84), 59
 Trischmann, H., 266
 Tritt, C., 34 (166), 61
 Tröger, J., 80 (39, 40, 41), 81, 82, 83 (40), 84 (39, 40, 42, 43), 85 (39, 41-44), 86, 90 (40), 92 (40), 94 (39, 40, 42, 43), 95 (40, 42, 43), 96 (41-44), 97 (39-41, 44), 99
 Trucco, F. S., 210 (126), 234 (126), 245, 344 (193), 359
 Tsao, M. U., 328, 338
 Tsarev, M. V., 122 (43), 127 (43), 155 (195), 193, 196
 Tschitschibabin, A. E., 41 (200, 202), 62, 217 (57), 225, 227 (57), 243
 Tschugaeff, L., 50 (245), 63
 Tsiang, T., 344 (166), 359
 Tsu, C. F., 114 (48), 118
 Tsuda, K., 125 (92), 178 (293, 295), 179 (296), 180 (295, 299, 301, 302), 181 (293, 295, 296), 182 (92, 293, 295), 194, 199
 Tunman, O., 210 (130), 245
 Tunmann, P., 212 (155), 245
 Turcotte, F., 121 (8), 122 (8), 123 (310), 124 (8), 126 (8, 310), 127 (8, 310), 130 (8), 163 (310), 166 (8), 174 (310), 175 (310), 176 (310), 186, 187 (8, 310), 190 (8), 192, 199
 Turner, R. B., 37 (176), 61
 Tutin, F., 250 (58), 253 (58), 270 (58), 310

U

- Ueno, M., 123 (48), 176 (48), 193
 Uffellie, O. F., 344 (194), 359
 Uhle, F. C., 258 (59), 261 (59), 310
 Ullmann, A., 318, 335
 Ulrix, F., 344 (179), 359

V

- Valeur, A., 123 (46), 125 (98), 156 (203, 204, 206), 157 (217, 218, 219, 222-248), 158 (251), 163, 174 (46), 190, 193, 194, 197, 198
 Valier, P., 125 (96, 97), 126 (96, 97), 194
 van Dorp, W. A., 3 (42, 54), 37 (42), 59
 van Hejningen, J., 2, 58
 Van Stolk, D., 391 (97), 393
 van Zijp, C., 344 (195), 359
 Veldsman, D. P., 249 (60), 253 (60), 270 (60), 310
 Venkatasubban, A., 155 (190), 196
 Viel, E., 210 (114), 244
 Vignoli, L., 344 (173), 359
 Vinet, A., 323, 336
 Virden, C. J., 342, 358
 Vitolo, A. E., 344 (190), 359
 Vogel, C., 302
 Vogt, A., 134, 135 (123), 195

Vogt, W., 203 (11), 205 (11), 242
 Volger, G., 38 (188), 47 (188), 62
 Vortmann, G., 3 (25), 58
 Voser, W., 296 (62), 312
 Voswinckel, H., 321, 336

W

Wachsmuth, H., 210 (113), 234 (113),
 244, 344 (167), 359
 Wackernagel, R., 157, 161 (208), 197
 Wael, H., 383 (58), 392
 Wagenaar, M., 210 (107), 234 (107), 244,
 383 (63), 393
 Wagner, A., 253
 Wagner, O., 45 (219), 47 (219), 62
 Wagner, R., 255 (6), 260 (6), 261 (6), 262
 (6), 309
 Wales, H., 210 (99), 212 (99), 244, 384,
 398
 Walker, J., 37 (177), 61
 Wallenfels, K., 251 (56), 258 (56), 260
 (56), 310
 Walpole, G. S., 319, 335
 Wang, C. Y., 112 (41, 42), 118
 Waser, E., 319, 323, 335, 336
 Wassmuth, H., 325, 336
 Watanabe, W. K., 318, 334
 Webb, L. J., 70 (19), 77 (19), 98
 Wehmer, C., 250 (61), 251 (61), 310
 Weichet, J., 345 (249), 360
 Weidel, H., 3 (41, 49, 55), 37 (41), 59
 Weil, Ruth A. N., 140 (142), 195
 Weir, M., 332, 337
 Weisenborn, F. L., 312
 Weissbach, K., 11 (88), 59
 Weisse, G. von, 210 (96), 244
 Welch, K. N., 225, 246
 Welsh, L. H., 31 (161), 61, 344 (201, 210),
 346, 347 (242), 348, 360
 Wendler, N. L., 15 (94), 29 (94), 30 (94),
 47 (94), 60
 Werle, E., 323, 336
 Werner, H., 55 (259), 63
 Wettstein, A., 158, 198
 Whetstone, R. R., 191 (327), 199
 Whipple, F. A., 383 (62), 393
 White, E. P., 121 (11, 12, 13, 30, 31), 122
 (11-13, 36-39, 41), 123 (13, 39, 62,
 63, 67), 124 (12, 13, 36, 39, 67), 125
 (36, 37), 126 (31, 37, 63, 103, 107),

127 (39), 128, 129 (12, 38), 143 (39),
 144 (38), 156 (63), 166 (11), 167
 (62), 175 (12), 176, 185 (36), 186
 (39), 189, 193, 194, 195, 317, 334
 White, H. L., 274 (19), 275 (19), 276 (19),
 306 (19), 307 (19, 63), 311
 Wickström, A., 344, 360
 Widmer, Angela, 161 (262), 198
 Widmer, R., 37 (179), 42 (179), 61, 124
 (76), 131 (119), 132 (119), 133, 158
 (119), 194, 195
 Wieland, H., 137 (129), 195
 Wight, N. J., 204 (14b), 242
 Williams, C. G., 3 (33), 58
 Williams, J. B., 344 (197), 359
 Williams, J. H., 112 (51), 116 (51), 118
 Willm, E., 2 (24), 58
 Willstätter, R., 131, 134, 135, 136, 157,
 161, 190, 195, 197, 198
 Wilson, S. D., 346, 348, 353, 360, 361
 Winekler, F. L., 2, 58
 Windaus, A., 203 (11), 205 (11), 242, 366,
 392
 Winstein, S., 44 (216), 62
 Winterfeld, K., 133, 136, 138, 139 (132),
 140 (144, 145), 141 (120), 142 (144,
 145), 143 (120, 159, 160, 161), 158,
 159 (257), 162 (267, 268), 163, 165,
 167, 169, 174 (253, 267, 268, 271),
 179, 187, 195, 196, 198
 Winterstein, E., 202 (4), 203 (12), 204
 (12), 205 (4), 243, 319, 335
 Wintersteiner, O., 274 (19), 275, 276
 (19, 65), 282, 284 (61), 286 (61),
 287 (61), 288 (61), 289 (61), 290 (20),
 292 (64), 293 (20, 66), 294 (66), 296
 (20), 299 (64), 306 (19), 307 (19), 311,
 312
 Wischnegradsky, A., 3 (39, 46), 58, 59
 Wisegarver, B. B., 70 (54), 83 (54), 99
 Witkop, B., 52, 54 (256), 63
 Wohl, A., 6 (68, 69), 26 (68, 69), 40 (68,
 69), 59
 Wolf, C. F., 112 (51), 116 (51), 118
 Wolfes, O., 123 (45), 174 (45), 193, 342,
 343, 348, 358, 359
 Wolff, P., 71, 98
 Wolfenstein, R., 157, 161 (208), 162, 163,
 197, 198
 Wompe, A. F., 226 (58, 59), 227 (58, 59),
 234 (59), 236 (59), 243

Woo, M., 339, 355
Wood, H. C. S., 376 (41), 380, 390 (102),
392, 394
Woodruff, E. H., 330 (128), 337, 353, 361
Woodside, J. M., 383 (62), 393
Woodward, R. B., 15 (94), 29 (94), 30
(94), 47 (94), 48 (233), 55 (260), 57
(267), 60, 63, 376, 392
Woolf, L. I., 204 (14b), 242
Work, T. S., 21 (119), 44 (216), 60, 62,
112 (39), 118, 296 (67), 312
Wright, C. D., 344 (212), 360
Wright, C. R. A., 272, 273 (68), 274 (68),
277, 297 (68), 298 (69), 312
Wu, C. K., 355, 362
Würtzen, V., 212 (146), 213 (146), 245
Wunschendorff, M. H., 125 (97), 194

Y

Yavel'berg, G. I., 127 (109), 195
Yoshida, S., 180 (301), 199
Yunusof, S., 343, 359
Yurashevskii, N. K., 317 (16, 17), 334

Z

Zaboev, S. A., 124 (72), 142, 194
Zakharkin, L. I., 390 (103), 394
Zalán, E., 26, 28 (150), 61
Zav'yalov, S. I., 232, 243
Zemplén, G., 249 (62), 251 (62), 310
Zohner, K., 124 (76), 131 (119), 132 (119),
133, 158 (119), 194, 195
Zorn, W., 2 (15), 19 (15), 58
Zwierzchowski, R., 21 (118), 22 (118), 60

SUBJECT INDEX*

A

N-Acetylemetine, 370
N-Acetyephedrine, 346
O-Acetyl-*d,l*-ephedrine, 346
N-Acetyl-*d-ψ*-ephedrine, 347
O-Acetyl-*d-ψ*-ephedrine, 347
N-Acetylmescaline, 328
Aconitum napellus, 343
 Acronidine, 78
Acronychia baueri, 70, 78
 Acronycidine, 70, 73, 74
*iso*Acronycidine, 73
 Acronycine, 79
Adhatoda vasica, 102
 Adrenaline, 313, 353
 Aegelenine, 70
Aegle marmelos, 70
 Δ^{16} -Allopregnen-3 β -ol-20-one, 268
 Allosolanidane, 255
 Aloperine, 173, 174
 Aminocytisine, 146
 Ammodendrine, 188
Ammodendron conollyi, 121, 126, 188
 Ammothamnine, 185
Ammothamnus lehmanni, 121, 125, 126, 185
 2-*n*-Amylquinoline, 80, 89
 Anabasine, 183
dl-Anabasine, 189
Anabasis aphylla, 121, 124, 183
 Anagyramine, 171
 Anagyrine, 130, 159, 169
Anagyris foetida, 121, 122, 124, 126, 170
 Andirine, 319
 Angelic acid, 273
 Angeline, 319
 Anhaline, 320
Anhalonium fissuratum, 320
Anhalonium lewinii, 324, 329, 331
 Anhydrolupinine, 134
 Anhydropilocarpic acids, 216
 Aphyllic acid, 184
 Aphyllidine, 183, 184
 Aphylline, 183

Arthrophytum leptocladum, 317
 1-Azabicyclo[4.4.0]decane, 120

B

Baptifoline, 187
Baptisia australis, 124, 126, 127
Baptisia exaltata, 122
Baptisia minor, 121, 122, 124, 126, 127
Baptisia perfoliata, 121, 122, 124, 126, 127, 130
Baptisia tinctoria, 122
 Baptitoxine, 144
N-Benzoylcorydaldine, 373
 Benzylmethanamine, 342, 349
Boletus edulis, 202, 204
Bothriospora corymbosa, 364
Bufo arenarum, 331
 1-*n*-Butyl-3,4-dihydroisoquinoline, 380

C

Calycotamine, 189
Calycotome spinosa, 121
d-Calycotomine, 189
 Candicine, 314, 320, 321, 331
Capirona decorticans, 364
Capsicum annuum, 251
 Carnegine, 323
Catha edulis, 343
 Cathine, 342
 Caulophylline, 144
Caulophyllum thalictroides, 124
 Cephaeline, 364, 378, 379
 Cevadine, 272
 Cevagenine, 273, 297
 Cevine, 273, 297
Chelidonium majus, 126
 Chlorolupinane, 135
 Chlorolupinine, 135
Chloroxylon swietenia, 69
 Cinchene, 4, 13
*apo*Cinchene, 13
 Cincholoipon, 5
 Cincholoiponic acid, 5, 40

* (Botanical names are printed in italics. Prefixes such as *nor*-, *iso*-, *apo*-, are printed in italics and disregarded for indexing purposes.)

Cinchomeronic acid, 3
Cinchona spp., 1
 Cinchonamine, 50
 Cinchonhydrines, 21
*apo*Cinchonidine, 20
 β -Cinchonidine, 20
 Cinchonidinone, 29, 45
 Cinchonine, 2
*apo*Cinchonine, 20
*hetero*Cinchonine, 33
 Cinchoninic acid, 3, 37
 Cinchoninone, 7
 Cinchotenine, 19
 Cinchotoxine, 9, 25, 45
 β -Collidine, 3
 Conquinamine, 50, 51
 Corydaldine, 367
 Coryneine, 314, 323, 331
 Corypalline, 323
 Cupreine, 22, 50
 Cuspareine, 80, 83, 90
 Cusparidine, 80
 Cusparine, 80, 82, 87
 Cytisamic acid, 152
 Cytisine, 129, 143, 159
 α -Cytisolidine, 147
 β -Cytisolidine, 147
 Cytisoline, 147
Cytisus austriacus, 123
Cytisus battandieri, 122
Cytisus bearii, 126
Cytisus canariensis, 122, 124
Cytisus caucasicus, 121, 123, 126
Cytisus grandiflorus, 126
Cytisus hillebrandtii, 122, 124
Cytisus kewensis, 126
Cytisus laburnum, 122, 123, 190
Cytisus linifolius, 121, 122
Cytisus monspessulanus, 122, 124, 125
Cytisus nigricans, 121
Cytisus proliferus, 121, 126
Cytisus ratisbonnensis, 123, 126
Cytisus scoparius, 123, 125, 126, 174, 318, 322
Cytisus sessilifolius, 123
Cytisus stenopetalus, 121, 122, 124
Cytisus versicolor, 126

D

Dehydrosparteine, 162
 Demissidine, 253, 258

Demissine, 252
 Deoxylupanine, 168
 Desoxyephedrine, 345
 Desoxyvasicine, 105
Dichroa febrifuga, 101, 112
 Dichroidine, 112
 Dichroine, 112
 Dictamnol, 73
 Dictamnol acid, 73
 Dictamnol, 69
*nor*Dictamnol, 72
 ψ -Dictamnol, 75
Dictamnus albus, 69
 Dihydroaphyllidine, 183
 Dihydrodesoxyvasicine, 105
 Dihydrojervine, 291
 α -Dihydrojervinol, 291
 Dihydroisojervinol, 295
 Δ^4 -Dihydrojervone, 291
 Dihydroquinotoxine, 45
 Dihydrorubijervine, 278
 Dihydrovasicine, 105
 2:4-Dihydroxyquinoline, 73
 Dilupine, 186
 6,7-Dimethoxyisoquinoline, 366
 6,7-Dimethoxyisoquinoline-1-carboxylic acid, 366
 6,7-Dimethoxy-1-keto-1,2,3,4-tetrahydroisoquinoline, 367
 4,5-Dimethoxyphthalonamide, 371
 4,5-Dimethoxyphthalonimide, 366
 Dimethylhistamine, 202, 203
 1:5-Dimethylimidazole, 221
 6,8-Dimethylquinoline, 148
 Diosgenin, 267
 Dipterine, 317

E

Echinocactus gibbosus, 324
Echinops ritro, 66
 Echinopseine, 66
 Echinopsine, 66
 β -Echinopsine, 66
 Emetamine, 364, 384
 Emetine, 363, 364
 Emetoline, 366
 Ephedrine, 342, 349
Ephedra alata, 341
Ephedra altissima, 341
Ephedra americana, 341

Ephedra distachya, 341
Ephedra equisetina, 341
Ephedra foliata, 341
Ephedra fragilis, 341
Ephedra gerardiana, 341
Ephedra helvetica, 340
Ephedra intermedia, 341
Ephedra monostachia, 342
Ephedra nebrodensis, 341
Ephedra pachyclada, 341
Ephedra procera, 341
Ephedra sinica, 341
 Ephedrine, 31, 339, 344
l-nor-ephedrine, 342, 348
d-nor-ψ-ephedrine, 342, 348
ψ-ephedrine, 31, 340, 347
Equisetum arvense, 124, 188
 Ergothioneine, 202, 203
 Eschlerine, 277
 2-Ethyl-4,5-dimethoxybenzoic acid, 374
 2-Ethyl-4,5-dimethoxyphenol, 374
 2-Ethyl-4-ethoxy-5-methoxybenzaldehyde, 379
 2-Ethyl-5-Methylpyridine, 248, 280
β-Ethylpyridine, 3
 Ethyltricarballic acid, 218
Evodia xanthoxyloides, 78
 Evodiamine, 101

F

Fagara coco, 69
Fagara mantchurica, 69
Fagara xanthoxyloides, 69
 Fagarine, 69
 Febrifugine, 101, 112
*iso*Febrifugine, 101, 112
Ferdinandusa elliptica, 364
Flindersia bourjotiana, 69, 78
Flindersia collina, 78
 Flindersiamine, 78
 Furoquinoline, 66

G

Galipea officinalis, 80
 Galipidine, 80
 Galipine, 80, 83, 85, 87
 Galipoidine, 80, 84, 90
 Galipoline, 80, 88
Genista aethnensis, 122, 125, 126

Genista ferox, 122
Genista humifusa, 121
Genista tinctoria, 121, 122, 124
Genista virgata, 122
Geodia gigas, 202
 Geoffroyine, 319
 Germerine, 274, 275
 Germidine, 275
 Germine, 275, 306
*iso*Germine, 306
β-Germine, 306
 Germitrine, 275
*neo*Germitrine, 276
Glycosmis pentaphylla, 69, 78

H

Halostachine, 314, 317, 330
Halostachys caspica, 317
m-Hemipinimide, 366
 Hercynine, 202, 203
Hermidium alipes, 323
Hillia tubaeflora, 364
 Histamine, 202, 203
 Histidine, 202
 Homothermopsine, 187
 Hordenine, 314, 320, 330
Hordeum sativum, 320
*hetero*Hydrocinchonine, 18
 Hydrohydrastinine, 323
 Hydroipecamine, 364
 Hydroxylupanine, 176
 3-Hydroxytyramine, 322

I

Ipecamine, 364

J

Jaborandine, 207
 Jaboridine, 229
 Jaborine, 207
ψ-Jaborine, 207
 Jervine, 270, 287, 290
*iso*Jervine, 295
 Δ^4 -Jervone, 291

K

1-Ketoquinolizidine, 140
 2-Ketoquinolizidine, 140

3-Ketoquinolizidine, 140
 4-Ketoquinolizidine, 140
 8-Ketosparteine, 166
 Kokusagine, 78
 Kokusaginine, 78

L

Laburnine, 190
Laburnum vulgare, 122, 129
 Leptocladine, 317
 Loiponic acid, 5
 Lupanine, 159, 166
d-Lupanine, 129
 α -*iso*Lupanine, 175
 Lupicaine, 142
 Lupinal, 142
 Lupinane, 133
*allo*Lupinane, 143
*nor*Lupinane, 120, 137, 138
 Lupinine, 128, 130
*allo*Lupinine, 143
*epi*Lupinine, 136
*epi*Lupininic acid, 136
Lupinus albus, 123, 124
Lupinus andersonii, 125
Lupinus angustifolius, 123, 176
Lupinus arboreus, 123, 126
Lupinus barbiger, 122, 126, 127, 129
Lupinus caudatus, 121, 123, 126, 127, 174
Lupinus corymbosus, 127
Lupinus hilarianus, 123
Lupinus kingii, 123, 129
Lupinus lanceolata, 122
Lupinus laxiflorus, 121
Lupinus laxus, 123, 126, 127, 177
Lupinus luteus, 124, 126
Lupinus macounii, 121, 123, 127, 185
Lupinus marianus, 125
Lupinus mutabilis, 126
Lupinus niger, 124, 126
Lupinus palmeri, 124, 125, 127, 128, 143
Lupinus perennis, 123
Lupinus polyphyllus, 123
Lupinus pusillus, 121, 123, 125, 126
Lupinus sericeus, 123, 125
Lupinus termis, 124
 Lupinylbarbituric acid, 142
Lycopersicum esculentum, 251, 253
Lycopersicum hirsutum, 253
Lycopersicum peruvianum, 253

Lycopersicum peruvianum chutatum, 253
Lycopersicum pimpinellifolium, 253

M

Mandelic acids, 352
 Matrine, 178
 Matrinic acid, 179
 Matrinidines, 180
Medicosma cunninghamii, 79
 Medicosmine, 79
Melicope fareana, 70
 Meroquinene, 4
 Mescaline, 314, 324, 331
 4-Methoxy-2-*n*-amylquinoline, 80, 89
 3-Methoxypyridine, 188
 6-Methoxyquinoline, 3
 1-Methyl-5-*n*-amylimidazole, 221
 γ -Methylcyclopentenophenanthrene, 248
 Methylcytisine, 144
 1-Methyl-6,7-dimethoxyisoquinoline, 371
N-Methylemetine, 367
N-Methylephedrine, 348
l-*N*-Methylephedrine, 342
d-*N*-Methyl- ψ -ephedrine, 342
N-Methyl- ψ -ephedrine, 349
 1-Methylimidazole, 220
N-Methylmescaline, 328
N-Methyl- β -phenethylamine, 317
 β -Methylpicolinic acid, 134
O-Methylpsychotrine, 364, 378, 379, 384
 3-Methyl-4-quinazolone, 106
 1-Methyl-2-quinolone, 80
N-Methyl-2-quinolone, 66
N-Methyl-4-quinolone, 66
 1-Methyl-1:2:3:4-tetrahydroquinoline, 68
N-Methyltyramine, 314, 319
O-Methyltyramine-*N*-methylecinnamide, 322
 Monolupine, 169
 Monspessulanine, 185
Moringa pterygosperma, 343

N

Niquidine, 21
*iso*Niquidine, 21
 Niquines, 21
 Nitrocytisine, 145

β -Nitrocytisine, 146
 Nitroso- ψ -ephedrine, 347
 4-Nonanone, 133

O

Octahydropyridocoline, 120
Orixa japonica, 69, 78
 Oxosparteine, 157
 Oxycytisine, 145
 Oxymatrine, 182
 Oxysparteine, 157, 160
 Oxytyramine, 314

P

Pachycarpine, 161
Pachycereus marginatus, 316
Panicum miliaceum, 320
 Peganine, 101
Peganum harmala, 102
 Pentalupine, 190
 Peyote, 314, 331
 Phenethylamine, 316, 317
 Phenyl-(4-quinolyl)-ketone, 42
Phoradendron californicum, 318
Phoradendron flavescens, 318
Phoradendron villosum, 318
Physoclaina orientalis, 251
 Pilocarpic acid, 215
*iso*Pilocarpic acid, 215
 Pilocarpidine, 207, 228
d-Pilocarpidine, 226
 Pilocarpine, 207
d-Pilocarpine, 226
*iso*Pilocarpine, 207
*meta*Pilocarpine, 224
*neo*Pilocarpine, 230
 ψ -Pilocarpine, 207
 Pilocarpoic acid, 219
Pilocarpus heterophyllus, 206
Pilocarpus jaborandi, 206
Pilocarpus microphyllus, 206
Pilocarpus pennatifolius, 206
Pilocarpus racemosus, 206
Pilocarpus spicatus, 206
Pilocarpus trachylophus, 206
 Pilomalic acid, 220
*homo*Pilomalic acid, 217
d-Pilopic acid, 225
*iso*Pilopic acid, 216, 217

*dl-iso*Pilopic acid, 225
*homoiso*Pilopic acid, 216, 217
*dl-homoiso*Pilopic acid, 225
*iso*Pilopininc acid, 223
 Pilosine, 207, 230
 Pilosinine, 232
 Piluvic acid, 217
Piptanthus nepalensis, 122
Podalyria buxifolia, 123, 124
Podalyria calyptata, 123
Podalyria sericea, 123, 124
 $\Delta^{5,16}$ -Pregnandien-3 β -ol-20-one, 267
 Protoveratridine, 274
 Protoveratrine, 275
 Protoverine, 276, 306
*iso*Protoverine, 308
 Pseudojervine, 272
Psychotria emetica, 364
Psychotria granadensis, 363
Psychotria ipecacuanha, 363
 Psychotrine, 364, 378, 379
 Purapuridine, 258
 Purapurine, 251, 258
 Pusilline, 173, 174
 Pyrrolizidine, 120, 191

Q

Quinaldine, 80
 Quinamicine, 53
 Quinamine, 50, 51
*apo*Quinamine, 53
 4-Quinazolone, 105, 112
 Quinene, 4, 13
*apo*Quinene, 13
*epi*Quinidine, 33, 50
*neoiso*Quinidine, 21
 ψ -Quinidine, 21
*apo*Quinidine methyl ether, 21
*iso*Quinidines, 20
 Quinidinone, 29
 Quinine, 2
 total synthesis, 48
*epi*Quinine, 50
*hetero*Quininc, 18, 50
*iso*Quinines, 21
 Quininic acid, 3, 37
 Quininone, 15
 Quinoline, 80
 Quinolinic acid, 134
 Quinolizidine, 120

4-Quinolyl-(2-pyrryl)-ketone, 44
 Quinotoxine, 9, 25, 45, 50
 Quinuclidine, 39
 Quitenine, 19

R

Remijia amazonica, 364
Remijia spp., 1
Retama sphaerocarpa, 125, 126
 Retamine, 173, 175
 Rhatanine, 319
 Rhombifoline, 188
 Rhombinine, 169
Richardsonia brasiliensis, 364
Richardsonia pilosa, 364
Roemeria refracta, 343
 Ruban, 47
 9-Rubanols, 47
 Rubatoxine, 47
 Rubijervine, 270, 277
*iso*Rubijervine, 270, 280, 312
 Rubremetine, 369
 Rutaecarpine, 101

S

Salsoline, 323
 Sarothamnine, 190
Sarothamnus scoparius, 126
 Sarsasapogenic acid, 258
 Sarsasapogenin, 258
Sida cordifolia, 342
Silybum marianum, 318
Skimmia japonica, 69
Skimmia repens, 69
 Skimmianal, 74
 Skimmianic acid, 74
 Skimmianine, 66, 69
 Solancarpidine, 258
 Solancarpine, 251, 258
 Solangustidine, 270
 Solangustine, 253, 270
 Solanidan-3 α -ol, 255
 Solanidan-3 β -ol, 255
 5 β -Solanidan-3 β -ol, 258
 Solanidan-2,3-diol, 256
 Solanidane, 278
 5 β -Solanidane, 255
 3 β -Solanidanol, 278
 Δ^4 -Solaniden-3 α -ol, 255

Δ^4 -Solaniden-3 β -ol, 255
 $\Delta^{2,4}$ -Solanidiene, 255
 $\Delta^{3,5}$ -Solanidiene, 255
 Solanidine, 253, 278, 312
 Solanine, 250
 Solanocapsine, 268
*apo*Solanocapsine, 269
 Solanosodine, 259
Solanum aculeatissimum, 251
Solanum asperum, 251
Solanum auriculatum, 252, 253, 270
Solanum aviculare, 252
Solanum bacciferum, 251
Solanum caavurana, 251
Solanum carolinense, 251
Solanum demissum, 252
Solanum dulcamara, 251
Solanum grandiflorum, 251
Solanum mammosum, 251
Solanum marginatum, 252
Solanum nigrum, 251
Solanum panduraeforme, 249, 253, 270
Solanum paniculatum, 251
Solanum peckoltii, 251
Solanum pseudocapsicum, 268
Solanum pulverulentum, 253
Solanum sodomium, 250, 251, 252
Solanum tomatillo, 251
Solanum torvum, 252
Solanum tuberosum, 250, 251
Solanum verbascifolium, 251
Solanum villosum, 251
Solanum xanthocarpum, 251
 Solasodamine, 252, 258
 Solasodane, 258
 Δ^4 -Solasoden-3-one, 259
 $\Delta^{3,5}$ -Solasodiene, 259
 Solasodine, 253, 258
 Solasonine, 251, 258
 Solatubine, 253
 Solatunine, 250
 Solauricidine, 269
 Solauricine, 253, 269
 Solmargine, 252, 258
 Sophocarpine, 178
 Sophochrysine, 190
Sophora alopecuroides, 121, 124, 125, 126
Sophora angustifolia, 124, 125
Sophora chrysophylla, 121, 122, 124, 125
Sophora flavescens, 124
Sophora microphylla, 122, 124, 125, 127

- Sophora pachycarpa*, 124, 125, 126
Sophora secundiflora, 122
Sophora tetraptera, 124, 125
Sophora tomentosa, 122
 Sophoramine, 186
 Sophoridine, 186
 Sophorine, 144
Sorghum vulgare, 320
 Sparteine, 156
l-Sparteine, 129
*pseudo*Sparteine, 163
 α -*iso*Sparteine, 174
Spartium junceum, 122, 126
 Spartyrine, 162
Stetsonia coryne, 323
 Surinamine, 319
- T
- Taxus baccata*, 342
 Tetrahydrodehydroemetine, 372
 Tetrahydrodesoxytyzine, 151
 Tetrahydrojervine, 291
 Tetralupine, 143
 Thermopsine, 186
Thermopsis lanceolata, 121, 122, 125, 126, 127, 187
Thermopsis rhombifolia, 121, 122, 124, 125, 127, 188
 Tiglic acid, 273
Tocoyena longiflora, 364
 Tomatidine, 267
 Tomatine, 252, 267
 Trichocereine, 328, 334
Trichocereus candicans, 316, 320, 321
Trichocereus lamprochlorus, 320, 321
Trichocereus spachianus, 322
Trichocereus terscheckii, 324, 328
- Trilupine, 177
 Tyramine, 313, 318
- U
- Ulex europaeus*, 121, 122, 127
 Ulexine, 144
 Umbelliferone, 112
 Urocanic acid, 204
- V
- Vanillylzygadenine, 277
 Vasicine, 101, 102
 Veralbidine, 277
 Veratramine, 270, 271, 272, 282
 Veratridine, 273
 Veratrosine, 271, 272, 282
 Veratrolyzygadenine, 277
Veratrum album, 272, 274, 275, 277, 280, 282, 290
Veratrum eschscholtzii, 277
Veratrum grandiflorum, 282
Veratrum sabadilla, 272, 273
Veratrum viride, 271, 274, 275, 276, 280, 282, 290
Virgilia capensis, 123, 124, 127, 186
 Virgilidine, 143
 Virgiline, 186
Viscum album, 317, 318
- Z
- Zanthoxylum americanum*, 322
 Zygadenine, 270, 277, 308
*pseudo*Zygadenine, 308
Zygadenus indermedius, 308
Zygadenus venenosus, 276, 308



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13
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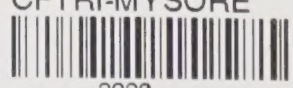
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